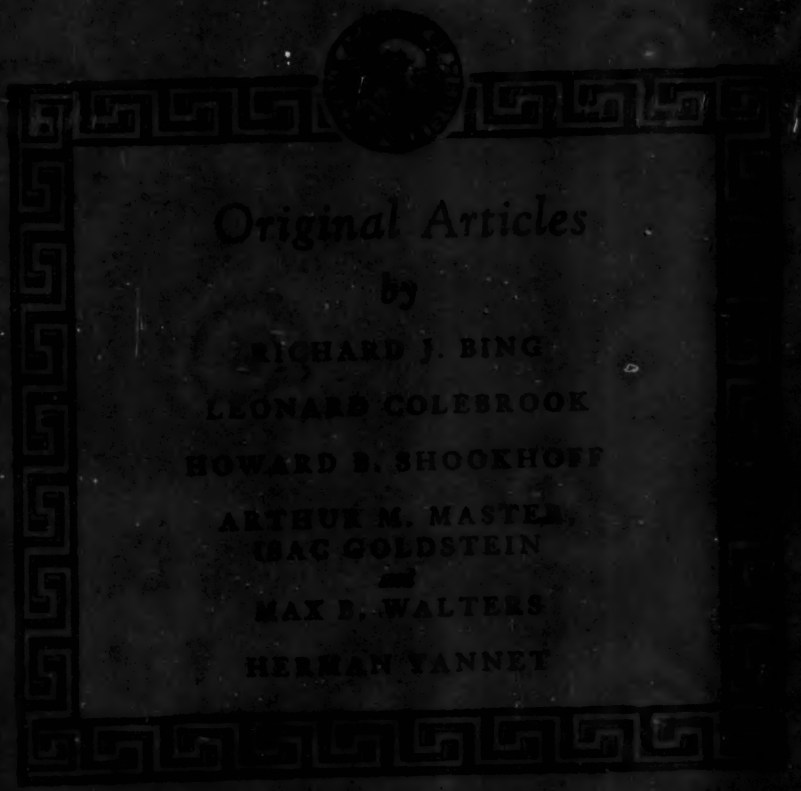
JULY 1951

BULLETIN

OF THE NEW YORK ACADEMY OF MEDICINE



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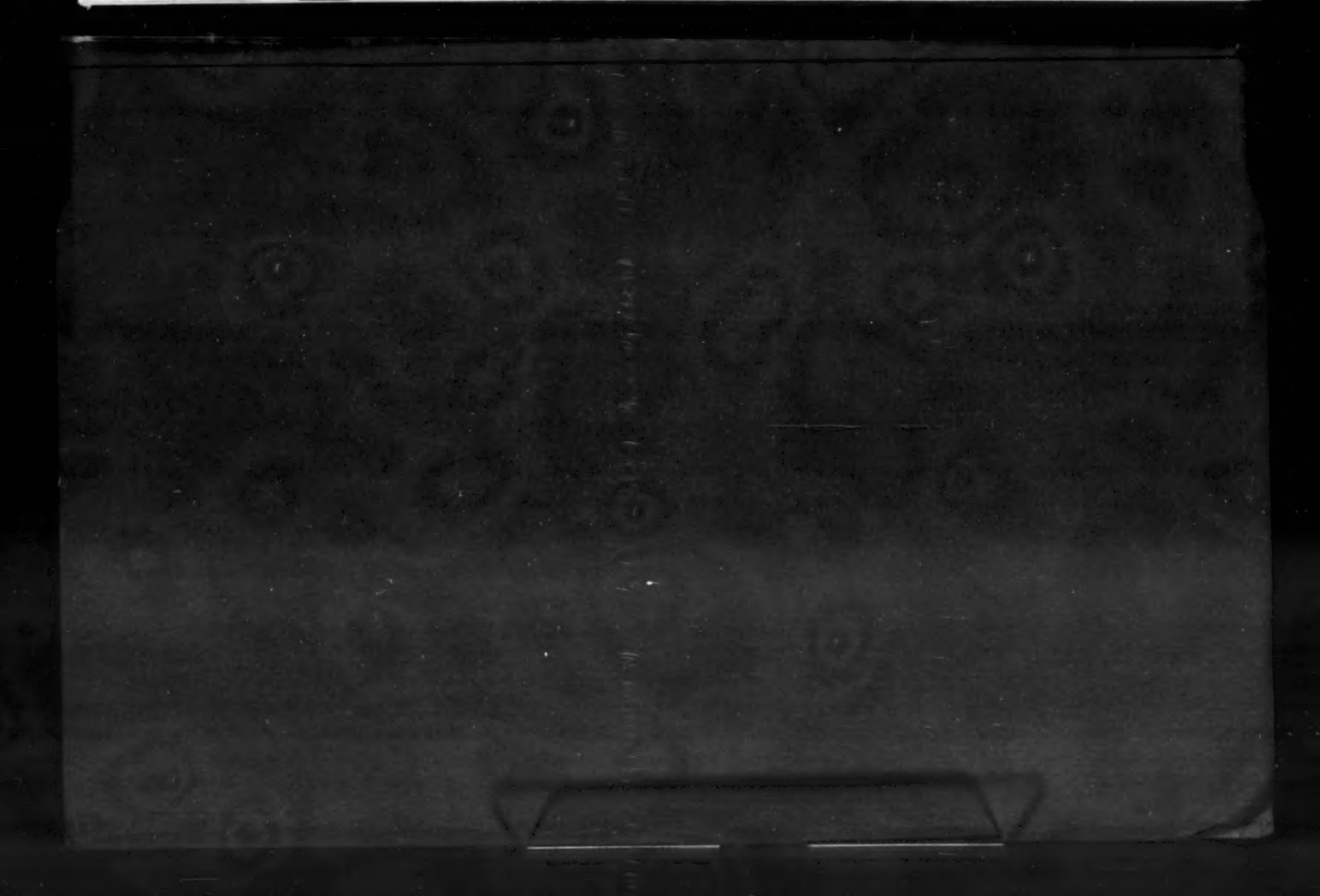

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1. Stritzler, C.; Fishman, I. M., and Laureus, S.: *Transactions New York Acad. Sc.*, *13*:31, Nov., 1950.

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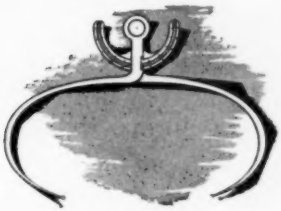

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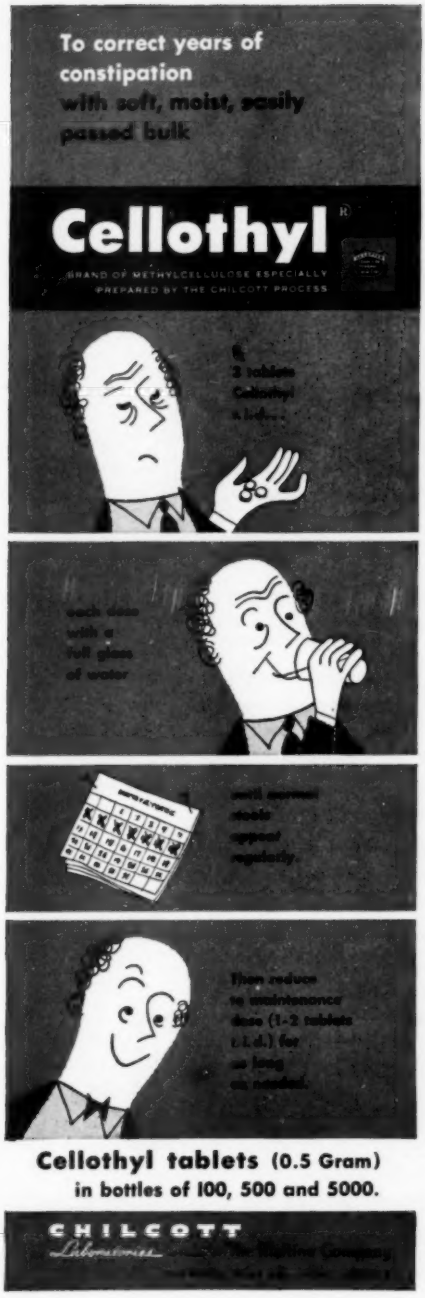
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1. Newey, J. A., and Goetzl, F. R.: Permanente Med. Bull. 7:67 (July) 1949.

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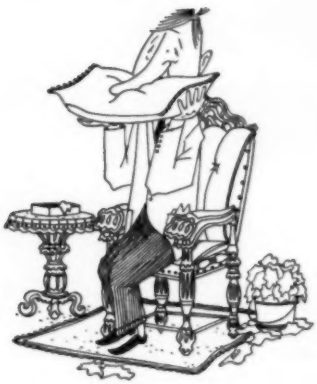

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MAHLON ASHFORD, *Editor*

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BULLETIN OF
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VOL. 27, NO. 7 JULY 1951

THE CORONARY CIRCULATION IN HEALTH AND DISEASE AS STUDIED BY CORONARY SINUS CATHETERIZATION*

RICHARD J. BING

Associate Professor of Surgery, The Johns Hopkins University

It is estimated that about four to eight million persons in the United States are afflicted with some form of heart disease. The figure for heart disease comprises about a third of the deaths from all causes and approximates the sum of the next three leading causes combined. The instance of mortality from heart disease must be based ultimately either on diseases of the coronary circulation or of the myocardium. It has been estimated that about 32 to 54 per cent of persons with organic heart disease die from disease of the coronary arteries.[1] This indicates the important role which coronary disease plays in the production of heart failure and sudden cardiac death. It also illustrates clearly that more attention should be centered on the coronary circulation by the physiologist and cardiologist alike.

Many methods have been described to study the coronary circulation. Until recently, these methods have been applied only to the isolated heart in vitro or to the open chest animal. Morawitz developed a cannula

* From the Department of Surgery, The Johns Hopkins Hospital and University, Baltimore, Maryland. Paper given before the New York Heart Association, February 27, 1951 at The New York Academy of Medicine.

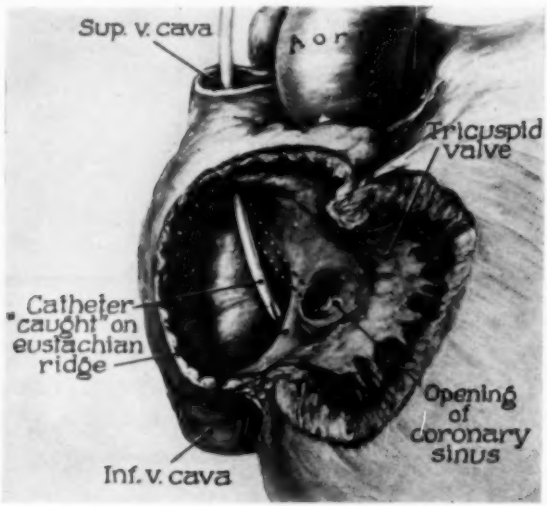

Fig. 1. The anatomical relationship of the coronary sinus. Difficulties in entering the coronary ostium are illustrated by showing the catheter caught on the Eustachian ridge (Courtesy of the Am. Heart J., Vol. 38, No. 1, 1949. The C. V. Mosby Co., St. Louis, Mo.).

for the insertion into the coronary sinus via the right atrium.[2] The flow through the cannula was presumed to quantitate total venous return from the coronary vessels. We know now that this assumption is not correct. Anrep,[3] and Katz[4] cannulated both coronary arteries, supplied them with blood under constant perfusion pressure and measured coronary inflow under a great variety of dynamic conditions. Peters and Visscher[5] and others measured coronary flow in the isolated heart, connected to an artificial lung. Wiggers was the first to employ the beating heart of the anesthetized open chest dog in which the coronary vessels were naturally perfused from the aorta.[6] Gregg[7] and Green[8] improved on these methods by recording blood flow with an orifice or rotameter. The advantage of these more recent methods is that they permit the registration of phasic changes in the coronary inflow. But these and similar procedures necessitate anesthesia, opening of the chest and, of course, are not applicable to man.

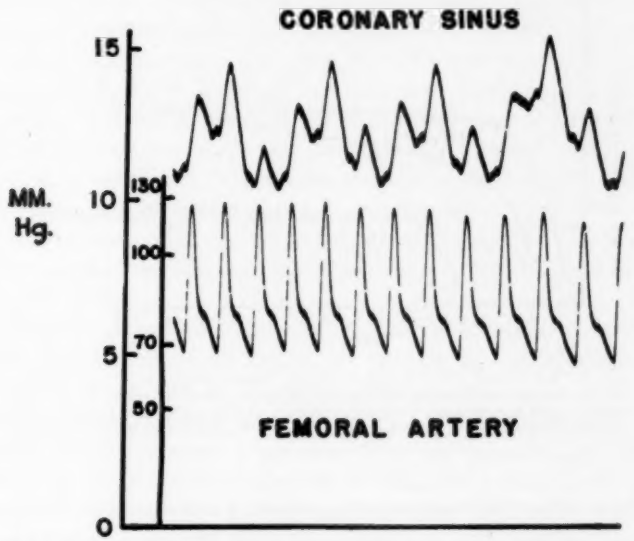

Fig. 2. Represents a simultaneous pressure tracing from the coronary sinus and the femoral artery. There are respiratory fluctuations in the coronary sinus pressure tracing.

The introduction of the nitrous oxide method for the determination of the cerebral blood flow by Kety and Schmidt[9] and of the catheterization of the heart by Cournand[10] suggested the possibility of applying these procedures to the determination of the coronary blood flow in man. In order to accomplish this it was first necessary to obtain samples of coronary venous blood. This problem was investigated by our group [11a] after workers at the Army Chemical Center and the University of Pennsylvania had shown that the procedure could be safely carried out in the experimental animal.[12, 13] In principle the method consists in the introduction of an intracardiac catheter through the right auricle into the coronary sinus, and the withdrawal of coronary sinus blood during or after saturation of the heart muscle with nitrous oxide.

Purposeful catheterization of the coronary sinus is not always easy. We are able to introduce the catheter into the coronary sinus in only about 40 per cent of all attempted catheterizations. The reason for this

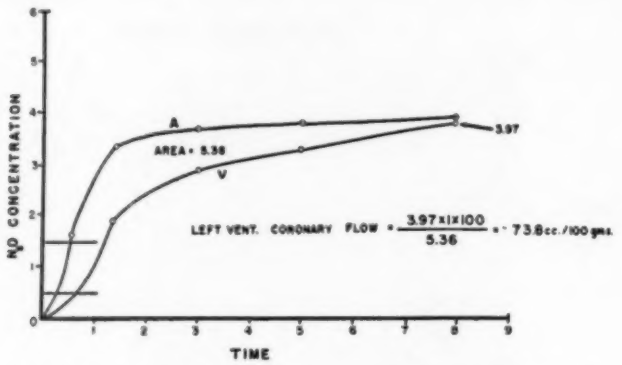

Fig. 3. Represents arterial and coronary venous nitrous oxide curves obtained during desaturation. Rising curves are obtained by subtracting each sample from the nitrous oxide concentration at full saturation (Courtesy of the Am. Heart J., Vol. 38, No. 1, 1949. The C. V. Mosby Co., St. Louis, Mo.).

difficulty is that the Eustachian ridge or the Thebesian valve overlies the coronary ostium (Fig. 1). These anatomical variations deviate the tip of the catheter away from the coronary ostium into the right ventricle or the inferior vena cava.[11a, 11b] It is usually not difficult to obtain proof of entry into the coronary sinus. The proofs consist in the unusual configuration of the catheter, particularly in the right lateral position and the dark color of the blood withdrawn which is the result of the low oxygen content of coronary venous blood. Furthermore, cardiac arrhythmias which are not too infrequent when the catheter is introduced through the tricuspid valve into the right ventricle are usually absent when the catheter is situated on the coronary sinus. Finally, the pressures obtained from the catheter in the coronary sinus are lower than those usually obtained from the right ventricle (Fig. 2). Thus, it is possible with a minimum of disturbance to the patient, to obtain samples of venous blood draining the myocardium.

Once the catheter has been placed in the coronary sinus, the heart is saturated with 15 per cent nitrous oxide. Simultaneous samples of arterial and coronary vein blood are drawn, and the N_2O contents during the saturation or, preferably, the desaturation, with nitrous oxide are plotted on plain graph paper (Fig. 3). The flow per unit of heart muscle may then be calculated.[11a]

It has become evident from the work of Gregg[7] that the coronary sinus drains primarily left ventricular muscle. Consequently, we measure with this method the coronary flow through a unit (100 grams) of the left ventricular tissue. It should be remembered, however, that although essentially all blood in the coronary sinus appears to arise from the left coronary artery, not all the left coronary artery inflow leaves by this channel.[7] Furthermore, Visscher has shown that the oxygen content of the coronary sinus blood does not necessarily represent that of the other venous channels draining the myocardium.[14] Therefore, we measure the blood flow through that unit of muscle only which drains into the coronary sinus.

Since the difference between the coronary arterial and the coronary sinus oxygen contents are known, we are able to measure the oxygen usage of that same unit of myocardium. O_2 usage cc./100 gm./min. = (O_2 content arterial blood volume per cent − O_2 content coronary sinus blood volume per cent) x coronary flow/100 gm./min. In order to obtain the oxygen consumption of the total left ventricle, this figure must be multiplied by the total left ventricular weight. O_2 usage left ventricle = O_2 usage/100 gm. left ventricle x $\frac{\text{left ventricular weight.}}{100}$

Heart weight can be approximated in normal hearts from tables of Smith which relate heart weight to total body weight.[15] The left ventricular weight is 53 per cent of the total heart weight. The oxygen usage (cc O_2) can now be converted into energy units (kilogram meters) because each cc. of oxygen corresponds to about two kilogram meters of energy.[16] Energy cost (left ventricle) = O_2 usage (cc O_2/min. x 2). The work of the left ventricle is then obtained from the accepted formula of Starling: Work (kilogram-meters per minute) = cardiac output (cubic centimeters per minute) x mean aortic pressure (cm Hg) x 13.6.[17] Only the pressure energy is calculated because the velocity energy of the left ventricle is relatively small. Energy cost of the left ventricle is then related to its work. This relationship represents the efficiency of the left ventricle: Mechanical efficiency (per cent) =

$$\frac{\text{work of left ventricle (kilogram-meters per minute)}}{\text{energy cost of left ventricle (kilogram-meters per minute).}}$$

The efficiency of the normal left ventricle is approximately 23 per cent; this means that 23 per cent of the total amount of energy which the heart takes in in the form of oxygen is converted into useful work.

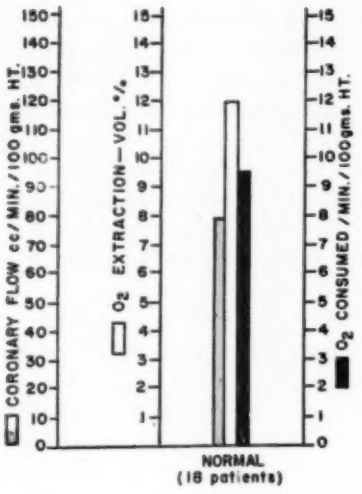

Fig. 4

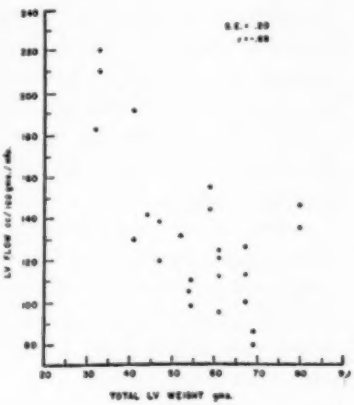

Fig. 5

Fig. 4. Shows the findings obtained in 18 normal individuals. It may be seen that the coronary blood flow through 100 grams of left ventricular muscle tissue is 77 cc., the oxygen consumption per 100 grams is 9.4 cc. The average oxygen extraction is 12 volumes per cent. These figures for coronary blood flow and oxygen consumption are slightly higher than those previously published by this author.

Fig. 5. Illustrates the relationship between the left ventricular blood flow per unit of left ventricular muscle to the total left ventricular weight. It may be seen that an inverse relationship exists between total left ventricular weight on one hand and the blood flow per 100 grams on the other (Courtesy of the Am. J. Physiology, Vol. 160, No. 1, 1950).

Some of the assumptions necessary in these calculations have already been mentioned. The calculations per unit of weight should be considered as reasonably accurate as Gregg and his co-workers have recently shown.[18] They found an average variation between the coronary flow/min/100 gm. as determined with the N_2O method and with the rotameter of $\pm$ 12.4 per cent.[18] The main assumptions arise when one attempts to calculate efficiency of hypertrophied hearts, because the heart weight cannot be accurately assessed in these patients. However, by using normal heart weights in patients with hypertrophied left ventricles, maximal values for efficiency are obtained, and if the maximal efficiency is low, true values must be even lower.[11a] This is the case in

myocardial failure. Furthermore, in assessing the effects of drugs upon the heart, individual percentages of efficiency are immaterial but the changes in per cent following the application of the drug are important. The method, therefore, enables us to examine the cardiac pump itself rather than the effect of the pump's action in the form of cardiac output and pressure.

Coronary flow and myocardial O_2 consumption in normal man: Figure 4 illustrates that the average coronary blood flow through 100 grams of left ventricular muscle tissue is 77 cc. The oxygen consumption of this unit muscle is 9.4 cc. of oxygen per minute. The average oxygen extraction is 12 volumes per cent. The large oxygen extraction of the heart muscle is striking, particularly if one contrasts it with the relative low coronary blood flow. If one converts figures for coronary blood flow obtained per 100 grams into values for coronary flow through the whole human myocardium, one finds that coronary blood flow represents only a relatively small fraction of the cardiac output (about 5 to 10 per cent). This is a small figure when compared with the large volume of blood which perfuses the kidney[19] or the liver.[20] The low fraction indicates that the heart satisfies its metabolic requirements not by a large flow but by a large oxygen extraction. The normal heart extracts even more oxygen than working skeletal muscle, where work has to be exhaustive before similar low levels of venous blood are reached.[21] The most important means by which the heart can cope with increased oxidative requirements is by increasing the coronary flow. It should be mentioned in passing that values for coronary flow obtained for the normal human myocardium are similar, weight for weight, to those found in anesthetized dogs with the nitrous oxide method[12] or in the open chest dogs with the rotameter.[7]

In the unanesthetized dog, however, the coronary blood flow per unit of heart muscle is greater than in man.[22] Figure 5 shows that an inverse relationship exists betwen the left ventricular flow per 100 grams and the total weight of the left ventricle. Smaller left ventricles have a relatively higher flow per unit of weight than larger ones. This relationship between blood flow and heart weight has been also observed by Cohn in the heart-lung preparation.[23] It is probable that the rate of coronary blood flow and of cardiac oxidative metabolism per unit of cardiac tissue is related to the surface area. It is generally accepted that metabolic rate is a function of the ratio of surface area to body

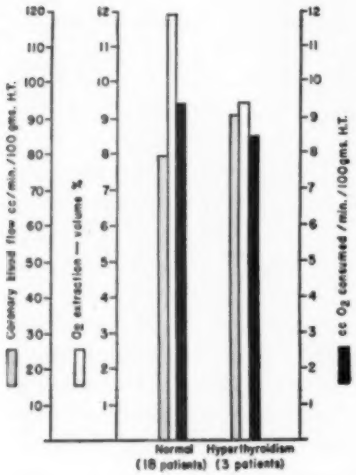
Coronary blood flow cc/min./100 gms. H.T.
O2 extraction — volume %
cc O2 consumed/min./100gms. H.T.
Normal (18 patients)
Hyperthyroidism (3 patients)

Fig. 6

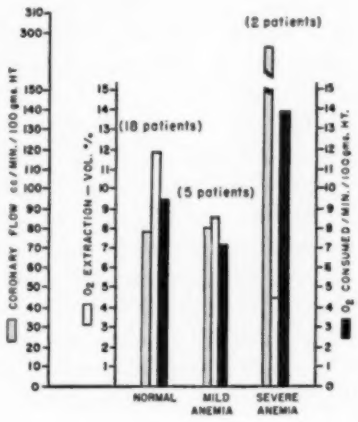

Fig. 7

Fig. 6. Compares the findings in normal individuals with patients with hyperthyroidism. In the latter group the coronary flow is slightly increased but the oxygen consumption per 100 grams of left ventricular tissue is reduced.

Fig. 7. Illustrates the finding in patients with mild and severe anemia. In the former group, the coronary flow is slightly increased, arterial venous oxygen difference is decreased. The oxygen consumption per unit of left ventricular weight is decreased. In severe anemia, however, the coronary flow is trebled, bringing the oxygen consumption of the heart muscle to even higher than normal values.

weight. As ventricular weight varies directly with body weight, the proportion of left ventricular weight to body weight is the same in small and large animals. Consequently, the metabolism of left ventricular muscle per unit weight should be determined by the ratio of surface area to left ventricular weight. As this ratio is higher in small animals, the cardiac metabolism per unit of heart weight is increased. In large animals the ratio of surface area to ventricular weight is low, and the coronary flow per unit of heart weight is less.[22]

The hyperkinetic heart: Three conditions belonging in this category will be discussed. They are: thyrotoxicosis, anemia and peripheral A-V fistula. Figure 6 shows surprisingly normal myocardial oxygen consumption per unit weight in Graves' disease, despite the increase in the total metabolism. The heart apparently does not share in this general

increase in the overall metabolic processes. Similar findings were obtained by Dock and his associates in the heart of thyroid fed rats.[24] They found that while both rate and weight of the heart of these animals were increased, the oxygen consumption per gram of heart muscle per beat was the same as in control animals. This points to an interesting contrast between the efficiency of the heart and that of the whole organism in thyrotoxicosis. It has been shown especially by Boothby[25] that the energy consumption per unit of mechanical work of patients with hyperthyroidism is greater than in normal individuals. Kommerell,[26] however, has demonstrated that the cost of each added kilogram meter of work is the same in the hyperthyroid patient as in normal individuals. This indicates that the efficiency of active muscular work in hyperthyroidism is of the same order as in the normal. It is probable, of course, that with hypertrophy of the heart, the total cardiac oxygen consumption is increased. But the fact remains that the oxygen consumption per unit of myocardial tissue is normal in hyperthyroid patients.

In patients with mild anemia (hemoglobin between 7 and 9 gm.) the coronary flow is slightly increased, the oxygen extraction and as a result the oxygen usage per unit myocardium are decreased (Figure 6). In some of these patients the oxygen extraction by the heart muscle is so complete that the coronary venous blood contains less than two volumes per cent of oxygen. With the first line of defense, the oxygen extraction, thus breached, the heart must rely entirely on an increase in flow to satisfy its metabolic requirements. To what extent this may happen can be seen from results obtained in two patients with severe anemia, who had a hemoglobin below 6 gms. Here the coronary flow trebled, bringing the oxygen consumption of the heart muscle to even higher than normal values (Figure 7).

In a patient with peripheral arteriovenous fistula without cardiac failure but with large cardiac output, the coronary flow and the oxygen consumption per unit of heart weight were increased (93 cc. blood/min/100 gm. and 10.2 cc. O_2/min/100 gm. respectively). This illustrates that increased load and large initial fiber length *can* lead to an increase in myocardial oxidative metabolism.

Hypertensive cardiovascular disease and coarctation of the aorta: Figure 8 illustrates that the coronary flow, the oxygen extraction and the cardiac consumption per unit of myocardium are normal in essential hypertension. Since the flow is normal, in the presence of increased

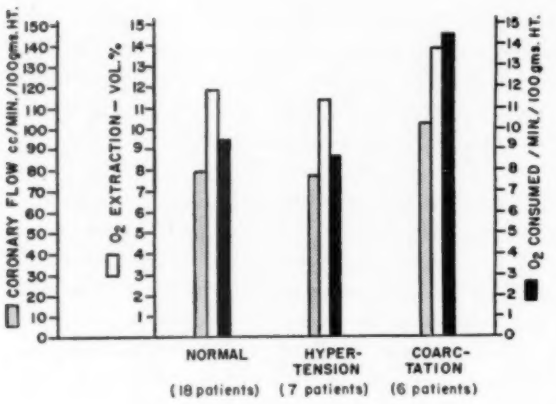

Fig. 8

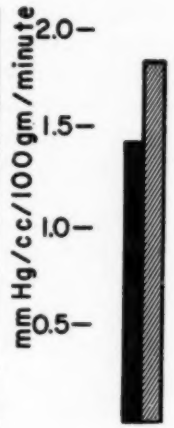

Fig. 9

Fig. 8. Compares the findings obtained in normal individuals to patients with essential hypertension and coarctation of the aorta. In essential hypertension the coronary flow, the oxygen extraction and the cardiac oxygen consumption per unit of myocardium are normal. In coarctation of the aorta, however, the coronary flow, the oxygen extraction and the myocardial oxygen consumption are increased.

Fig. 9. Compares the coronary resistance per unit of left ventricular muscle in normal and hypertensive patients. The vascular resistance per unit of myocardial weight of patients with essential hypertension is increased.

aortic and coronary pressure, the vascular resistance in the coronary bed per unit of left ventricular weight is increased (Fig. 9). A similar increase in the vascular resistance has been found in the cerebral and renal vessels.[27, 28] It will be shown that in coarctation of the aorta the coronary vascular resistance /100 gm. of left ventricular muscle is normal. Since the coronary blood flow per unit of left ventricular weight is normal and since the left ventricle is hypertrophied in patients with essential hypertension, the coronary flow and the oxygen consumption per total left ventricular muscle must be increased above normal. This is illustrated in Figure 10 which demonstrates a completely different response of the heart subjected to chronic and acute increases in load, respectively. When the heart is exposed to *acute* increases in load, the coronary blood flow and the oxygen consumption per unit of weight increase. In the hypertrophied heart which is exposed to a *chronic*

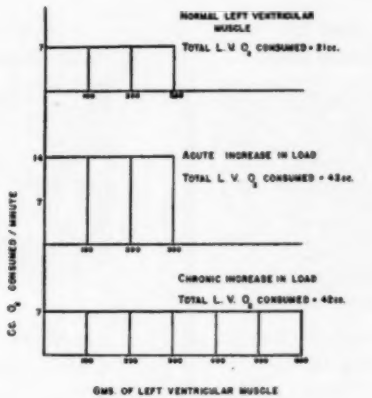
NORMAL LEFT VENTRICULAR MUSCLE
TOTAL L. V. O_2 CONSUMED = 21cc.
ACUTE INCREASE IN LOAD
TOTAL L. V. O_2 CONSUMED = 42cc.
CHRONIC INCREASE IN LOAD
TOTAL L. V. O_2 CONSUMED = 42cc.
CC. O_2 CONSUMED / MINUTE
GMS. OF LEFT VENTRICULAR MUSCLE

Fig. 10. Compares the response of heart muscle to acute and chronic increase in load. An acute increase in load results in increased oxygen usage per unit of fiber. A chronic increase in load results in a rise in the oxygen uptake of the whole heart, while the oxygen consumption per unit of weight remains constant (Courtesy of the Am. Heart J., Vol. 38, No. 1, 1949. The C. V. Mosby Co., St. Louis, Mo.).

increase in load, the coronary blood flow and the oxygen consumption per unit fiber are normal, but because of hypertrophy the total coronary flow and O_2 usage are increased.[11a] Thus, we have here a physiological expression of the economy of hypertrophy and an example of the significant difference with which the heart reacts to acute and chronic changes in load. Another interesting finding on hypertrophied hearts is related to the problem of how cardiac hypertrophy affects the myocardial blood supply. It has been shown by Roberts and Wearn[29] that in cardiac hypertrophy the average fiber diameter is increased. The average number of muscle fibers supplied by a capillary is still the same as in normal hearts, but the capillary concentration per unit of muscle weight shows a definite decrease which is caused by the enlargement of the muscle fibers. As the fibers enlarge the capillaries are pushed apart and the capillary concentration decreases in direct proportion to the increase in the diameter of the muscle fiber. Hypertrophy then appears to differ from normal growth in that in the latter the capillaries multiply and keep pace with the muscle as it grows while in hypertrophy the capillaries do not multiply. In the hypertrophied heart, the

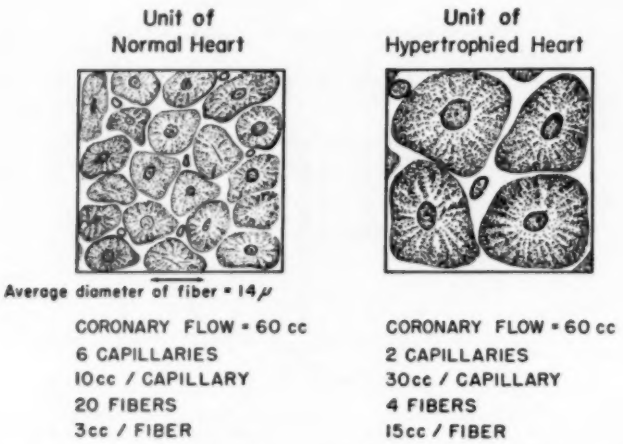

Fig. 11. Cross section of normal and hypertrophied myocardium. The volume of blood coursing through each capillary of a hypertrophied heart is greater than in the normal. Consequently, each fiber is supplied with a larger amount of blood.

coronary blood flow and the oxygen consumption per unit of myocardium are normal. This illustrates that the volume of blood coursing through each capillary in the hypertrophied heart must be greater than in the normal heart and that each fiber must be supplied with a larger amount of blood (Figure 11). There is, therefore, an increased flow through the individual capillary and increased irrigation of each individual myocardial fiber (Figure 11). These may be compensatory phenomena. The increased flow through each capillary does not mean that the hypertrophied heart is not put at a disadvantage. Hill[30] has found that the rate of oxygen diffusion through the tissues varies with the space of distance traversed which suggests that if cardiac fibers are hypertrophied, they might suffer from relative anoxia.

The findings in coarctation of the aorta are quite different from those obtained in essential hypertension. It may be seen from Figure 8 that flow and oxygen extraction and the myocardial oxygen consumption are all increased. Crumpton et al.[31] have shown that in coarctation of the aorta there is also an increased cerebral flow. These findings are

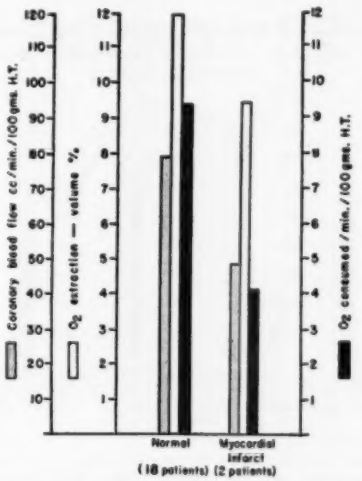

Fig. 12. Results obtained in 3 patients with myocardial infarcts. The oxygen extraction and oxygen consumption as well as the coronary blood flow per unit left ventricular tissue are reduced.

further evidence of the difference in mechanism of hypertension of the essential type and hypertension accompanying coarctation of the aorta. Since many of the individuals with coarctation were adults, the increased flow per unit weight was probably not due to the smaller heart size. The findings that the coronary blood flow in patients with coarctation is increased agrees with the results of Gupta and Wiggers and their group.[32] They found that resistance to coronary flow decreases when the resistance in the aorta is suddenly increased, partly as a result of mechanical reasons and partly through local action of metabolites. Therefore, the coronary channels carry a large fraction of the flow that is prevented from leaving the aorta through a stenotic orifice. This, incidentally, insures a better blood supply to the hyperactive heart.[32]

Myocardial fibrosis: The results obtained on three patients with myocardial infarcts are illustrated in Figure 12. It may be seen that in the patients who had electrocardiographic evidence and a history of myocardial ischemia or infarction, the O_2 extraction and O_2 consumption as well as the coronary blood flow per unit left ventricular tissue

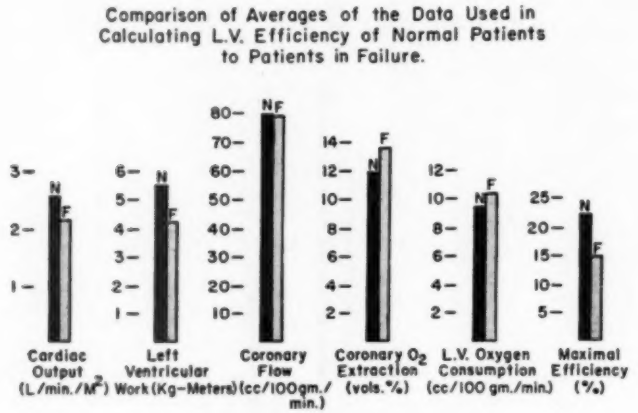
Comparison of Averages of the Data Used in Calculating L.V. Efficiency of Normal Patients to Patients in Failure.
N
F
Cardiac Output (L./min./M²)
Left Ventricular Work (Kg-Meters)
Coronary Flow (cc/100gm./min.)
Coronary O₂ Extraction (vols.%)
L.V. Oxygen Consumption (cc/100 gm./min.)
Maximal Efficiency (%)

Fig. 13. Illustrates that in failure the cardiac output and the left ventricular work are decreased, but the coronary blood flow is normal. It is of particular importance that the oxygen consumption per unit of heart weight is only slightly increased and that the maximal efficiency of the failing heart is diminished.

were reduced. This suggests that a considerable amount of scar tissue must have been perfused. Apparently the oxidative metabolism of scarred areas of myocardium due to infarction or diffuse fibrosis is considerable less than that of normal heart muscle. More work in this line is desirable, particularly because of the importance of comparing the reduction in oxidative metabolism with the electric manifestations of myocardial disease.

The behavior of the myocardium and the coronary circulation in cardiac failure: Figure 13 illustrates that in failure due to rheumatic, arteriosclerotic or hypertensive heart disease, the cardiac output and the left ventricular work is decreased but the coronary flow is normal. In this respect, the heart seems to react differently from other organs of patients in failure. In the brain, Scheinberg[27] has shown that the increased oxygen extraction in failure is not commensurate with the lowered blood flow. The kidney in failure has both decreased blood flow and increased oxygen utilization.[33] But the failing heart seems to maintain its coronary blood flow rather well.

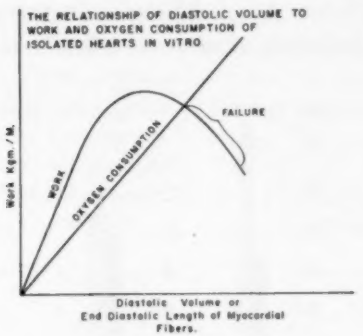
THE RELATIONSHIP OF DIASTOLIC VOLUME TO WORK AND OXYGEN CONSUMPTION OF ISOLATED HEARTS IN VITRO
FAILURE
WORK
OXYGEN CONSUMPTION
Work Kgm. / M.
Diastolic Volume or End Diastolic Length of Myocardial Fibers.

Fig. 14. The relationship of the diastolic volume to the work and oxygen consumption of the acute failing heart in vitro.

It is of particular interest that the oxygen consumption per unit of heart weight is only slightly increased in failure (Figure 13). Since the work of the left ventricle is decreased, the maximal efficiency of the failing heart is diminished. This decrease in cardiac output was present in patients with mitral valvular disease as well as in those with hypertensive and arteriosclerotic heart disease. In mitral disease with regurgitation the cardiac output is probably too low because of regurgitation of blood through the incompetent valve. In the other types of failure, however, figures for cardiac output are probably correct and the reduction in the maximum efficiency is entirely due to an actual reduction in systemic flow.

These findings illustrate that there is a marked difference between the metabolic response of the failing heart in vivo and the failing heart in vitro. Figure 14 shows that heart muscle shares with other types of muscle the characteristic that an optimum exists beyond which further stretching reduces the force of the contraction.[34] It may be seen that an increase in stretching of the muscle is indicated by changes in the diastolic volume. The work of the heart fails as the fibers overstretch. But the oxygen consumption of the heart in vitro continues to rise as the heart fails. In the failing human heart the oxygen consumption is not very different from the normal. This indicates that the essential disability of the failing heart in vivo consists of an inability to convert

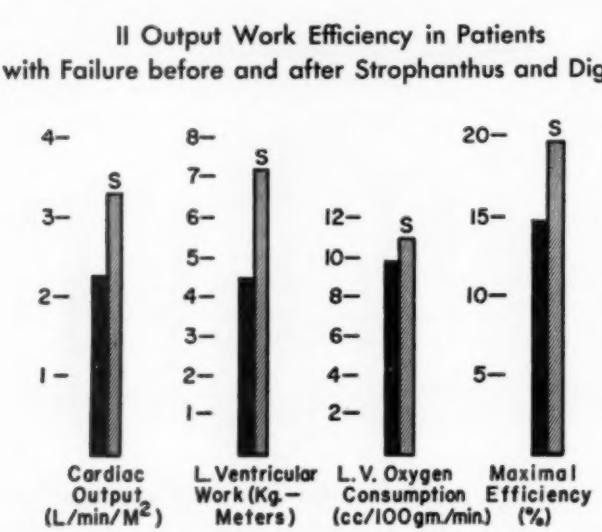

Fig. 15. Shows that strophanthus and digitalis preparations increase the work of the heart but have no effect on the oxidative myocardial metabolism. Thus, they increase cardiac efficiency only by an increase in cardiac work.

oxidative energy into useful work. There is a deficiency in the utilization of energy liberated through oxidative processes. It appears, therefore, that our concepts of the relationship between the initial fiber length and the oxygen consumption of the heart muscle need revision. It is entirely probable that as long as the heart is not in failure increased diastolic fiber length leads to increased O_2 usage per unit weight. Once chronic failure has developed, the oxygen consumption of the myocardium is normal despite increased diastolic fiber length.

From this discussion of the behavior of the coronary circulation and the oxidative metabolism in failure, the action of cardiac glycosides may be anticipated. Since the heart in failure seems to be unable to convert oxidative energy into useful work, the drugs must, in order to be effective, act to re-establish the link between energy consumption and energy liberation. Figure 15 shows that strophanthus and digitalis preparations increase the work of the heart by raising the cardiac output.[35] The glycosides, however, have no effect on the oxidative myocardial metab-

olism. They increase cardiac efficiency only by an increase in cardiac work and not by reducing oxidative metabolism.

The results of these studies point out a way for future research which has as yet been little explored. The fact that in cardiac failure the link between energy consumption and energy utilization is deficient suggests that the major disturbances in cardiac failure may lie in the contractile elements of the myocardial fibril directly. An application of Szent-Györgyi's work on skeletal muscle[36] to the contractile elements of cardiac muscle might prove of great value in future investigations of cardiac failure.

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THE PREVENTION OF BURNING ACCIDENTS IN ENGLAND AND AMERICA

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THE first six months of the war in Korea brought death to approximately 6,000 men of the U. S. Forces. Few people will realise that almost as many civilians die in a similar period each winter in the U. S. A. from burning and scalding accidents.

The actual figures for 1948 (12 months) given in "Accident Fatalities in the United States" published by the Federal Security Agency, were:—

4,593 deaths from "accidental burns"
3,075 deaths from "conflagrations"

I am informed that the last figure does not include the many deaths due to burning which were associated with accidents to automobiles, trains, ships and aeroplanes. These are computed at about 3,000 a year, making a gross total of about 11,000 for the whole year—or approximately 5,500 for half a year.

The number of non-fatal, but severe, burns among civilians is not known, but it may be roughly estimated at ten to fifteen times the number of deaths classified under "accidental burns," i.e., at from 45,000 to 70,000 for the whole United States. (The actual figure depends, of course, upon the interpretation of the word "severe" – it is probable that the number of burns *requiring admission to hospital* is much higher than 70,000). It must be remembered too, that the majority of these non-fatal cases have to undergo a prolonged and painful illness – and all too often recover with some permanent disability.

The care of all these severely burned people (usually for at least 50 days) involves the occupancy of a very large number of hospital beds, (in England we estimate the figure to be about one million hospital bed-days a year) with the services of doctors, nurses and a host of ancillary personnel.

And their recovery introduces a new social problem which is apt to

* Being the substance of a lecture delivered at The New York Academy of Medicine on 23rd December 1950.

be overlooked. Prior to 1940 it was uncommon for a burn of more than 30 per cent of the body surface to recover, but today, thanks to better treatment of shock and the greater control of infection by penicillin, etc., it is not uncommon for burns of 50, 60 per cent, or even more, to recover – and the proportion of such recoveries will certainly increase. In spite of the great advances of plastic surgery it can hardly be expected that the majority of these patients – half of whom are children – will survive as normal individuals, without some degree of disability or deformity, and often, in consequence, some economic handicap. The children who grow up in this way, as sub-efficient and unhappy people, will constitute a steadily increasing proportion of the general population.

For these reasons, as well as the avoidance of a great loss of life and much suffering, a serious attempt should be made to reduce the number of the accidents.

The object of this communication is to report to you on a study of the problem in England, and on some impressions I have formed while visiting your country.

The Problem in England

In trying to find out the circumstances in which our burning accidents have occurred – and how they might have been prevented – I have studied data from two sources, viz:

1. the Registrar General's Annual Reports of deaths. (H. M. Stationery Office, London.)

2. an analysis of 1,000 consecutive cases admitted to the Medical Research Council's Burns Unit of the Birmingham Accident Hospital during the three and one-half year period, 1945-48. This series included non-fatal as well as fatal burns and scalds. It was reported at length by Colebrook and Colebrook (1949).[1]

The outstanding facts which have emerged from these two studies are as follows:–

From the Registrar General's Reports of Deaths

(a) The annual loss of life from burns has decreased fourfold during the past forty years, in spite of a steady increase of the population. The number of deaths in 1908 was 2,650; in 1948 it had dropped to 670. Fig. 1 shows this remarkable decline expressed graphically in the form of death rates per million of the population. It seems probable that the falling rate since 1938 has been due more to the introduction of the sul-

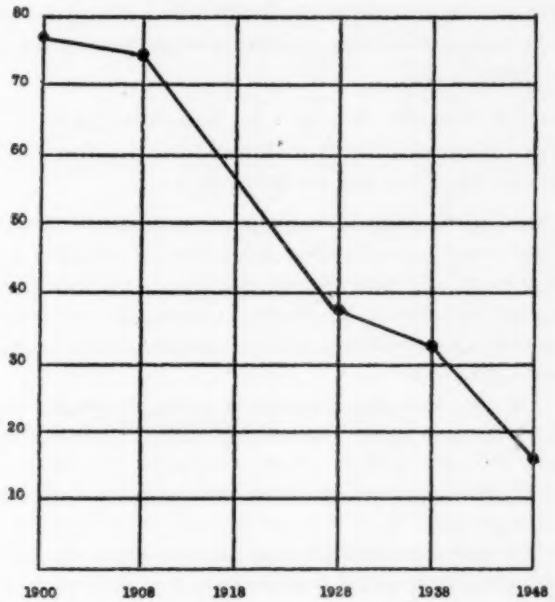

Fig. 1—Death rate (per million of population) from burns and scalds in England and Wales during first half of this century. (The figure for 1918 was not obtainable).

phonamide drugs and penicillin than to a large reduction in the number of accidents. While this decline is very satisfactory I believe there is still room for improvement; many of the 670 deaths in 1948 should not have occurred.

(b) Child deaths have always formed a large proportion of the total loss from burns (40 to 50 per cent). In the age group five to fourteen there are many more deaths from accidental burns among girls than boys (154 to 50 during the three years, 1946-48).

(c) The absolute number of deaths among old people (65 and over) has decreased during the past fifteen years—from about 350 a year to about 250—in spite of the steady increase of that age group in the population. But the death rate per unit of population continues to be higher than that of any other age group. (158 per million during 1947/48.)

(d) Deaths from "conflagrations" (buildings on fire) amounted to only 4 per cent of the total deaths from burning during the years 1900 to 1947 (3,769 out of 90,789). Children were the victims in 15 per cent of these deaths.

Facts derived from the study of 1,000 *consecutive case histories of patients admitted to the Birmingham Accident Hospital* 1945-48. (*Fatal and non-fatal cases.*)

(a) Although Birmingham is a highly industrialised city no less than 70 per cent of the burned patients who required admission to hospital had been burned in or about their homes; only 30 per cent were burned while engaged in industrial production. (Among the 303 burning accidents reported upon by Brown et al. in Glasgow (1945)[2] only 17.2 per cent were industrial.)

(b) The Case Mortality Rate among the 699 "domestic" burns (6.3 per cent) was much higher than among the 301 industrial cases, (1.3 per cent).

(c) 70 per cent of the domestic accidents happened to children (ages 0 to 14).

(d) The domestic accidents were almost equally divided between burns and scalds. (360 and 339 respectively.)

(e) Among the 360 domestic burns, in just over 50 per cent the injury was due to ignition of the patient's clothing by contact with a heating appliance (coal, electric or gas fire); or by the patient falling on to such a source of heat. In nearly every case the heating appliance concerned was without an adequate guard at the time of the accident.

It is noteworthy that of the 134 cases in which clothing was ignited 88 were females (with 35 deaths, = 41 per cent) and only 46 were males (with 5 deaths, = 11 per cent).

The most important causes of the 171 accidents which were *not* associated with heating appliances were: burning by flammable liquids—thirty-four cases; bonfires, fireworks, etc.—twenty-five cases; electrical burns—sixteen cases; hot fat and hot metal—each fifteen cases.

(f) Children were the victims in 80 per cent of the 339 scalding accidents which occurred in or about the home. And in this group of children (277 in number) no less than ninety were injured by the spilling of hot tea. Next came the group of seventy-nine children injured by "other hot liquids"; and then a group of forty-two scalded in their baths.

TABLE I—MORTALITY RATE FROM ACCIDENTAL BURNS AND SCALDS
(Conflagrations excepted)

	Year	*Deaths from Burns*	*Population (approx.) Millions*	*Deaths per Million*
Sweden	1947	70	7	10
England and Wales	1938	1266	41	30
	1948	620	43.5	14
Australia	1941	154	7	22
	1947	150	7.5	20
France	1945	1102	37	29.8
U.S.A.	1943	5951	134	44
	1947	4685	144	32.3

Summary of English Experience

Fire hazards are considerably greater in the homes than in industry.

Ignition of clothing by contact with an unguarded heating appliance, i.e., coal, electric or gas fire, was responsible for the most severe burns. The fact that this accident happened almost twice as often to females as to males, and carried a much higher death rate, strongly suggests that the nature of the clothing worn by females was an important contributory factor.

Scalding by hot water and other fluids was responsible for a very large number of injuries to children, which were, however, less severe than the burns. Boys were more often scalded than girls.

THE PROBLEM IN THE UNITED STATES

I have obtained data with regard to *fatal* burning accidents from:

(a) The Annual Reports of the Census Bureau.

(b) "Accident Fatalities in the United States" published by the Federal Security Agency, Washington, D.C.

(c) "Accident Facts" published by the National Safety Council, Chicago.

(d) "Accidental Deaths in Tennessee for Five Years 1939-43" published by the Tennessee Dept. of Health, Nashville.

The chief points which emerge from these reports are as follows:

1. The death rate for "accidental burns" (i.e., excluding conflagra-

TABLE II—DEATHS FROM CONFLAGRATIONS IN RELATION TO TOTAL DEATHS FROM BURNING ACCIDENTS

	1937	*Per cent of total*	1947	*Per cent of total*
ENGLAND and WALES				
Conflagrations	73	5.5	105	11.1
Accidental burns	1266		838	
Total	1339		943	
U.S.A.				
Conflagrations	2775	32	3315	41
Accidental burns	5951		4685	
Total	8726		8000	

tions) is considerably higher in the United States than in England and Wales and the Scandinavian countries. (See Table I.) Although the death rate has fallen during the last few years the decline has not been so marked as in England and Wales.

2. The proportion of child deaths to the total deaths from burns tends to be rather lower than it is in England. Thus, during 1947 and 1948 the children's deaths (ages 0 to 14) were 30 per cent of the total in the United States, whereas in England they were 43.5 per cent.

3. As in England the proportion of deaths among people aged 65 or more is high. These deaths accounted for 23 per cent of the total deaths from burning during 1947-48. The death rate (per million of persons of this age group at risk) was no less than 175 (approx.).

4. The death rate among the colored population has always been considerably higher than among the whites. Thus, during 1947-48 it was approximately 130 per million of the colored people at risk, as compared with 45 per million of the white population.

5. The deaths attributed to "conflagrations" are remarkably high in the U.S.A. by comparison with those so classified in England. *(See Table II.) The respective death rates for the two countries in 1948 were 21 and 1.2 per million.

* It is possible that the systems of classification in the two countries are not quite identical.

Why there should be this great difference will be discussed later. Meanwhile it may be noted that in recent years the death rate for men over 65 (from conflagrations) has been twice as high as that for women of the same age. (Thus in 1948 the rates per 100,000 were 5.2 and 2.1 respectively for the age group 65-74.)

Data with regard to all burning accidents—non-fatal as well as fatal—have been obtained from the published reports of Hoffman, of 1,000 consecutive cases at Cook County Hospital Chicago (1942)[3]; that of Low on 135 cases at the Boston Children's Hospital (1937)[4]; and from information sent to me by the Red Cross with regard to cases treated at Jackson County Hospital, Kansas City. In addition I am indebted to Drs. Neal Owens and Ricketson of New Orleans, and to Dr. Charles Lund of Boston for information as to the causes of burning accidents in their practice.

From all these sources I have gained the impression that the factors responsible for domestic burns in the United States vary somewhat widely in the different regions. Thus in New York I was told that many serious burns were due to the ignition of clothing by gas cooking stoves. In other cities, where natural gas is not available, I gather that the same accident is more often due to mishaps with kerosene stoves.

By and large, however, it appears that the problem is similar in our two countries. Flame, in one form or another, is the immediate exciting cause of the most severe burns. In the series of 1,000 consecutive burns and scalds reported by Hoffman from Chicago no less than 379 burns were attributed to flame. And of the 586 fatal burns and scalds analysed by the Tennessee Department of Health (1939-43) no less than 292 were traced to an "open grate" or a stove.

Summarising the information I have obtained, the predominant causes of burns in the United States appear to be:

Gas and kerosene stoves, and open grates burning wood or coal.

Careless use of kerosene for lighting or reviving fires.

Careless use of flammable liquids, e.g., for cleaning clothes.

Matches and cigarettes, especially in bed.

Firecrackers, fireworks and trash fires.

Hot fat and hot metals.

Chemicals.

Electrical burns.

In the first four categories the actual injury was usually caused by the ignition of clothing.

Scalds in the United States, as in England, are most often due to the upsetting of some hot liquid, such as tea or coffee, by very young children.

Preventive Measures

It would be improper for me, as a visitor to your country, with only a superficial knowledge of the problem, to suggest what is needed to reduce the number of these burning accidents, but I may perhaps tell you what tentative impressions I have formed, and what questions have arisen in my mind.

First, what could be done to reduce the very high wastage of human life from "conflagrations" in your country? Why should the death rate from these disastrous happenings be seventeen times that of England?

Everywhere I am told that it is due to the structure of your frame houses and that the fire hazard is greatly increased because they are so thoroughly dried out by central heating. It has been suggested to me also that the central heating plants themselves are sometimes responsible for starting fires; and in other cases the electrical installations. I am sure your Fire Services have abundant information on all these matters. If it is true that you are paying so high a price (in human life) for your policy of building frame houses is there not a strong case for changing that policy? Or could fireproofed materials be more widely used for the interior structures in which fires usually start? Do the Insurance Companies give special rates for brick-built houses?

Second, how far could the great number of "accidental" burns (i.e., those not associated with a "conflagration") be reduced by elimination of their chief causes? I am impressed by the fact that those causes are not widely known, even among medical men. When I have asked about these things I have usually been told that cigarette smoking in bed (plus alcohol) was largely responsible. But those who gave me that answer did not realize that 30 to 40 per cent of the deaths occur in young children. They were reflecting impressions derived from newspaper headlines.

As a preliminary to reduction of the accidents I think it will be essential for medical men who treat burns in different parts of the country to collect more data as to causative factors, and to bring them

repeatedly to the notice of the public. In Birmingham, England, we have found that aggregation of our burns and scalds in one hospital has greatly facilitated such enquiries and the public of the whole country has become much more "burn conscious" as a result.

That, I think, must be the first step in prevention—to make the public aware of the problem—and the medical men should take the lead in that process. Once the chief causes of the accidents have become known, the appropriate preventive measures will suggest themselves.

They will probably fall into three categories, as they have in England, namely:

Better design of heating appliances, and of fireguards.

Substitution of safer clothing materials (for children and old people) for the dangerously flammable fabrics now commonly used.

Better design of containers of hot liquids (tea and coffee pots, saucepans, etc.); and a nation-wide campaign among women's organizations and schools to prevent scalding accidents to children.

Better design of heating appliances and of fireguards.

The fact that many accidents are attributed to stoves and open grates suggests that there is room for improvement in the design of those appliances—at any rate for houses in which there are children. But I am not sufficiently familiar with your appliances to know in what respects they are dangerous, nor how those dangerous features could be eliminated.

In respect of guards on movable electric fires you are certainly far ahead of us in England. I have seen no reference in your burns literature to accidents associated with these fires. In England they are unhappily very common, because, in spite of many tragedies, most of our fires are still sold without an adequate guard.

The menace of flammable clothing materials

This is seldom mentioned in your burns literature but it lies at the heart of the burns problem. In England at any rate, it is undoubtedly true that many serious burns result from the momentary contact of a garment—usually a nightdress or frock made of flannelette, or winceyette or viscose rayon—with some heating appliance. Two or three seconds' contact is sufficient to ignite the material and the flame travels in a few more seconds over a large part of the garment. That could not happen with a less flammable fabric such as wool or silk. *It is the rapid burning*

of the clothes that leads to the extensive burning of the body. To reduce our deaths from burns (and the incalculable suffering of the non-fatal cases) we have got to concentrate upon the burning of clothes—and the guarding of fires which leads to it.

A few years ago American public opinion was strongly stirred by the deaths of several children whose cowboy suits caught alight while they were playing round a bonfire. The suits were made of a dangerously flammable long-pile rayon. I am told that damages amounting to something like 10 million dollars were awarded against those who had manufactured and marketed that material; and that, in consequence, none of your big stores would carry such material today.

That particular hazard has been effectively dealt with, but the problem still remains—and indeed on a much larger scale. Hundreds of children are terribly burned every year, and many lives lost, because their clothing catches fire. How many of them were wearing dangerously flammable clothing? That question is seldom asked—and we do not know the answer to it, because nobody has yet published any data as to the kinds of material most commonly associated with burning accidents. Nor is there, at present, any agreement as to what constitutes a "dangerous" degree of flammability.

But any person of ordinary intelligence can decide for himself about some of the materials in common use. It does not need an elaborate scientific test. If he hangs up a piece of well-dried flannelette or viscose rayon and holds a match to its lower edge for two to three seconds he will see it catch alight, and the flame spread rapidly over the whole sample within half a minute or less. It does not require much imagination to realize what would happen to a child wearing a frock made of that material. With pure wool or silk and some kinds of nylon the result will be entirely different—the material usually does not ignite at all, or it may glow and the glow spread very slowly, and then go out spontaneously after a few seconds.

To anybody who has carried out such a rough test it must appear astonishing that materials which burn so readily are being freely sold in every store all over the world without any warning to the public that they are flammable, and may constitute a danger to children. We have been shutting our eyes to this hazard and have lost thousands of valuable lives in consequence. If we are to deal with it effectively in the future we need, I think, a three point programme:

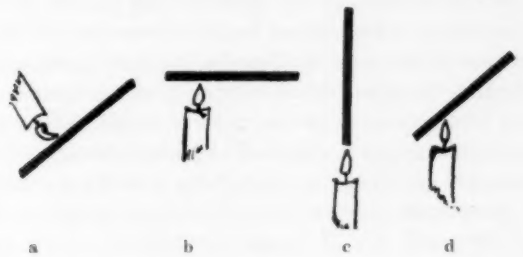

Fig. 2

1. We should collect actual data as to the kinds of fabrics which are most commonly associated with burning accidents. In England we have started to do this. Samples of unburned material are submitted by Coroners and certain hospitals for examination by a textile expert—both for identification and a flammability test. Within a year or so it should be clear which fabrics are usually associated with burning accidents. Without anticipating the verdict of that enquiry one may say that it is already evident that raised cotton fabrics will stand high in the list—probably at the top. It might not be the same in U.S.A. but I rather suspect that it will be.

2. We should reach agreement—if possible international agreement—on a carefully standardised method of assessing the degree of flammability of textiles. On the face of it that should not present great difficulty, but in fact it is by no means easy to devise a suitable method *for this purpose*. If the test is to reflect the relative degree of safety or danger of a given material *when made up in a garment and worn upon a child's body* it must indicate, not only the *readiness to ignite*, but also the *speed* at which flame spreads over the sample under test. That will vary much with the set-up of the test. Thus, if the fabric is held at an angle as in Fig. 2a, and the flame is directed downwards upon it (as in one test that has been proposed); or if the fabric is held horizontally with the flame vertical below it as in Fig. 2b, ignition of the material and spread of the flame will occur much less readily than it does when both the fabric and the flame are vertical as in Fig. 2c. I suggest that the arrangement shown in Fig. 2d approximates most closely to the conditions obtaining in the majority of domestic accidents.

This difficulty in devising the optimal set-up for the test is closely connected with that of the observer's personal reaction to a given result. To one observer it will seem obvious that the rapid ignition and spread of flame across a sample of fabric in the laboratory must mean that a child whose frock was made of that material would be in grave danger if it came into contact with a flame. To another observer that danger is not so obvious or so emotionally disturbing. Perhaps his imagination is less lively—at any rate he hesitates to translate the laboratory result into danger on the hearth rug. To meet this difficulty it will perhaps be necessary to devise a second method of testing, or rather a method of demonstration, such as draping the material on a dummy figure carried slowly past the standard flame on a moving platform. Destruction of half or more of the test garment within a few seconds could hardly fail to carry conviction as to its dangerous character.

Flammability tests have been described in the past in the following publications, but no one of them has so far gained general acceptance:

"What is Non-inflammable Flannelette," Lancet 2:175, 1911.

"British Standards Institution" Publication No. 476, 1932 London.

R. W. Little "The Inflammability of Textile Fabrics." Reinhold Publishing Co. 1947.

3. Having decided which of the materials in common use are so dangerously flammable as to constitute a serious hazard to young children wearing garments made of them, we ought surely to take such steps as will eliminate, or greatly reduce, that hazard. In effect we must aim at the use of safer materials for the clothing of all children (and old people), particularly for garments which stand away from the body, such as night dresses, dressing gowns and children's frocks. First it will be necessary to make such materials available in the shops at a price which people of moderate means can afford, and then, by wise propaganda, to encourage the buying of these materials even if they cost a little more than the dangerous ones, as they inevitably will.

Unfortunately that apparently reasonable policy is not so simple as it appears at first sight. Cotton fabrics will almost certainly rank high among the flammable materials most commonly used for children's clothes, and mothers will not readily change to other materials, even if these are available. Cotton fabrics have immense advantages. They are cheap, they wear well, they can be boiled, and when "raised," as in flannelette, they have a pleasant warm-to-the-feel quality. To replace

them by any other textile, even for the limited purpose of children's clothing, would cause a considerable economic disturbance in the world.

The best hope, perhaps, is that by further research, they may be rendered appreciably less flammable by treatment with flame-resistant or actually fireproofing chemicals.

Many methods of doing this have been proposed (albeit not usually with children's *clothing* in view) and for some it has been claimed that their effect on flammability withstood the usual laundering processes, and that they did not spoil the "handle" and wearing qualities of the materials. Certainly one or two processes have come near to this ideal, but when fabrics treated by them were offered to the public the latter did not seem inclined to "buy safety." I suggest that that may have been because the public as a whole is not alive to the danger of burning accidents. Education and propaganda will be essential preliminaries to the popularising of safer clothing. Meanwhile the need for continuous research into better fire-proofing methods remains—it should indeed be a matter for high priority in view of the possibility of an atomic war.

When the cost of carrying out these methods is under consideration it should be set against the financial loss at present incurred by the deaths of hundreds of children every year and the reduced efficiency of those who survive, as well as by the very large expenditure on hospital care for the burned people.

Conclusions

To reduce the number of our burning accidents in England it is clear that we must:

(a) Secure the better guarding of all heating appliances in homes where there are young children and old people.

(b) Provide less flammable clothing materials than those now in use for children and old people—and, by giving the public the facts about fire hazards, persuade them to buy these safer materials.

In America it seems probable that the number of deaths from conflagrations could be greatly reduced by changes in your building practices; and that many of your accidental burns (chiefly in the homes) could be eliminated by attention to the design of heating appliances and the introduction of safer clothing materials for children and old people. Propaganda by the press, by radio and television, by the cinema, and perhaps best of all by the influence of doctors, nurses and welfare per-

sonnel, should help to counteract carelessness with matches, cigarettes and flammable liquids.

In both countries the very numerous scalding accidents to children could be reduced by improving the design of containers of hot liquids (tea and coffee pots and cups, saucepans, etc.) so that they are less readily upset; and again by wisely planned, and not boring, propaganda, to make the public more aware that these mishaps can happen.

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THE PRESENT STATUS OF ANTIBIOTICS IN THE TREATMENT OF PROTOZOAN DISEASES*

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ENDAMOEBA HISTOLYTICA

Of the protozoan infections to which the human flesh is heir, the most wide-spread are malaria and amebiasis. Thanks to the active attention of a large group of scientists and technologists, and to the development of effective therapeutic and insecticidal agents, malaria is being slowly squeezed out of existence in those areas in which adequate programs are in effect. Amebiasis, on the other hand, may actually be spreading. At the very least, we are recognizing it with increasing frequency, and we are becoming more and more aware of its great prevalence.

Control of amebiasis in areas such as this in which we practice is not possible without a program of detection and treatment of cases. A considerable degree of insurance against amebic infection, as well as against other enteric infections, is provided by the protection of the water and food supplies. But the disease remains endemic even when environmental sanitation has reached a high level of perfection, owing to its transmission by foodhandlers. This transmission involves not only professional but also non-professional foodhandlers, such as housewives and domestic workers. Education of the population, and especially foodhandlers, in good personal hygiene diminishes the frequency of this person-to-person transmission. But inevitable human error makes this control imperfect. Effective treatment of the infected individuals affords more absolute protection. Thus, effective therapy is important not only to the physician and his patient but also to the community.

Bacitracin: In the field of protozoology, antibiotics were first employed on behalf of the parasites rather than against them. In the effort

* Presented before the Stated Meeting of The New York Academy of Medicine, December 7, 1950.

to improve the results of cultures of Endamoeba histolytica for diagnostic and experimental work, these agents were added to the media. E. histolytica will not grow in the absence of bacteria.* Nor will it grow well in the presence of too many bacteria. To bring about partial inhibition of bacterial growth first penicillin, and subsequently other antibiotics, were tried. Satisfactory results were obtained with penicillin and streptomycin. With bacitracin, however, it was observed that at certain concentrations, the amebas died off more rapidly than the bacteria.[1] Accordingly, bacitracin was tried in the most available experimental animal, Homo sapiens. Given by mouth, it was found to have a definite effect on E. histolytica infections.

The first cases were treated by Longacre.[2] A more elaborate study was then carried out by Most, Miller and Grossman.[3,4] These workers treated fifty-five patients with bacitracin. Some were followed for as little as one month; one half were followed for at least six months. There were seventeen failures as determined by the finding of parasites in the stools on follow-up examination. Re-treatment of some patients with one or two additional courses of bacitracin reduced the total number of failures to thirteen, or about 25 per cent. Ten patients who received adequate doses showed positive stools within one month of treatment. This high percentage of early relapse and the overall failure rate of 25 per cent compare unfavorably with the results obtainable with standard amebacides such as diodoquin and carbarsone.

At the Tropical Disease Diagnostic Service, we have treated twenty-five cases of E. histolytica infection with bacitracin.** We have been able to follow twenty-two of them for periods varying from one month to twenty-three months. There were five failures, all observed within two months of the treatment. One was re-treated with a higher dose and apparently cured.

The average follow-up period in the eighteen cases in which cure was eventually accomplished was five months. Six cases were followed for more than six months. All cases followed have had one or more examinations of the stools, each examination including post-cathartic specimens examined in the fresh state. This type of examination is essential if one is to get the highest proportion of positive results. An average

* Actually, E. histolytica has now been grown in association with Trypanosoma cruzi. (Phillips, B. P. and Rees, C. W., Am. Jour. Trop. Med. *30*:185, (March) 1950.)

**We are indebted to Dr. Harold W. Brown, Professor of Parasitology, Columbia University School of Medicine, for prompting this investigation, arranging for a supply of the antibiotic and suggesting dosage. The bacitracin was supplied by the Upjohn Company, Kalamazoo, Michigan.

of two examinations per case was done; an average of three satisfactory warm stools plus additional fresh and casual formed stools were studied per case.

Despite the fact that our dosage level was somewhat lower than that of Most and his associates, our results were comparable. We used 60,000 units daily for five days in all but three cases; in these three treatment was continued for ten days. One of the three was a failure. Most and associates used 80,000 units or more daily for ten days in almost all their cases. It is possible that our cases were somewhat less severe on the average.

Most and his associates report that symptoms were relieved even in those cases in which parasitologic cure was not obtained. They state that those patients whose stools were temporarily negative did not have a recurrence of symptoms when the organisms again appeared in the stools. They refer also to one case in which bacitracin was the only one of the available amebacides which would control the relapses. In our series, three out of four eventual failures had symptoms. One was partly relieved and two completely relieved despite the fact that E. histolytica persisted in the stools.

Aureomycin: The first published reports on aureomycin in amebiasis were those of Most[5] and McVay, Laird and Sprunt.[6] Follow-up reports by these investigators[3, 7] and our own experience, have convinced us that aureomycin achieves results comparable with those obtainable using the standard amebacides, carbarsone and diodoquin. Most[3] reports failures in only two of thirty-three cases, most of them mild, followed for periods ranging from two weeks to approximately a year. McVay[7] reports failure in four of twenty-three cases followed for periods ranging from one to six months. We have treated twenty-four cases and have followed twenty-one of them for periods ranging from one to twelve months. To date we have had but two failures. In both of these, diodoquin had previously failed. The cases of McVay and his associates were evidently more severe on the average than ours, and probably those of Most and his associates. This would explain the somewhat higher failure rate.

The average follow-up period in our cases was four and one-half months. In each case we carried out an average of four and one-half stool examinations, each including two satisfactory purged stools and usually a casual specimen in addition.

The effect of aureomycin on the clinical manifestations is frequently good even when the laboratory findings indicate parasitologic failure. Hughes[8] reports almost uniform clinical improvement in a series of cases of more than average severity, many of them failures with standard drugs. In twenty-seven of his thirty-eight cases, stools were negative at the end of two months. But most of the others were markedly improved symptomatically. We have observed this improvement of symptoms in a slightly different way. In two patients who had had diodoquin with some improvement and whose stools were negative, troublesome intestinal symptoms persisted. They were dramatically relieved by the administration of aureomycin.

Terramycin: Most and Van Assendelft[9] have reported favorable results with terramycin in amebiasis. Their report, however, must be taken as preliminary since the follow-up period was extremely brief. They treated twenty-two cases and followed them for periods ranging from one day to three months. Only three were followed for more than one month. One failure was reported. But in ten patients, no fresh stools were examined in the follow-up period.

Our own early results are less encouraging. We have used somewhat smaller doses than Most and Van Assendelft, but they are similar to those we have employed with aureomycin. So far, we have treated six cases with doses ranging from 4 to 8 Gm. in four to five days. Two patients, both children under ten years of age, received 4 Gm. in four days and still showed E. histolytica in the stools. One was immediately re-treated with 6 Gm. in four days and became negative and remained so during a follow-up of one month. Excluding the child successfully re-treated we have two failures among our six cases. The cases have been followed for one to two months.

It is, of course, too early to arrive at a conclusion as to the relative merits of terramycin and aureomycin, but it is my impression that the latter is more effective at lower dosage levels. In one patient who has had recurrent symptoms following an amebic infection, aureomycin produced more complete and lasting relief than terramycin in equivalent doses.

Penicillin: In our enthusiasm for the newer antibiotics we tend to lose sight of the fact that penicillin, although actually beneficial to the growth of E. histolytica in the test tube, can be of great value to the patient with amebiasis. Hargreaves,[10] in 1945, reported on fifty-seven

cases of resistant amebiasis, showing the remarkable improvement which could be achieved with penicillin. He recommended the use of sulfasuxidine as well, but pointed out that penicillin alone could bring about a fall of temperature to normal in twenty-four hours and formed stools in forty-eight. The stools, of course, usually continued to show amebas. Armstrong, Wilmot and Elsdon-Dew[11] have reported similar results in Africa. They have been able to observe partial or complete healing of ulcers, visible through the sigmoidoscope, following treatment with penicillin and sulfasuxidine only. A higher rate of apparent cure was obtained when these drugs were given together with standard amebacides, than when the amebacides were given alone. Hargreaves, too, found that his resistant cases became amenable to amebacides following treatment with penicillin and sulfasuxidine. Additional reports of similar results are to be found in the more recent literature, and the writer has personally observed cases in which penicillin alone has produced dramatic improvement.

It is possible that the combination of aureomycin or bacitracin with such drugs as carbarsone and diodoquin would be more effective than any of these individually. However, data on this subject are not yet available. In fact, it is difficult to decide whether we should combine anti-bacterial with amebacidal therapy in all cases, or limit it to those which are relatively severe or have relapsed.

Untoward Effects of Antibiotics: It is important not to let our enthusiasm for new therapeutic agents make us neglect to record the untoward effects. The intramuscular administration of penicillin, and the oral administration of bacitracin, aureomycin, and terramycin appear to involve no serious toxicity. But the course of therapy with these agents does not always run entirely smooth. Comment on the side effects of penicillin would be superfluous. Bacitracin is somewhat dangerous if used parenterally but when given by mouth, there is no risk, since there is little if any absorption.[3] In our experience, the side effects are mild and rarely disturbing to the patient. Some of them were elicited only by questioning and close observation. They affect primarily the gastrointestinal tract and the skin. Thirteen of the twenty-four patients had symptoms probably referable to the drug. Four had abdominal pain; two had epigastric distress; one, anorexia; one, nausea; and two, anal itching. Four had transitory skin eruptions usually on the face or arms, which disappeared before therapy was complete. Three patients men-

tioned headache. In no case did we have to stop therapy because of its side effects.

Aureomycin is more apt to distress the patient. The most common side effects are anal itching or irritation, nausea and vomiting, diarrhea, and sore tongue. We have studied a group of thirty-four cases with respect to side effects; this includes the twenty-four patients treated with aureomycin alone plus another ten with a history of amebiasis to whom aureomycin was administered at a time when the stools were negative as a result of previous therapy with other drugs. Nausea occurred in eleven cases, but in only one did it necessitate stopping treatment. However, if larger doses had been used this complication might have been more frequent. Diarrhea occurred in seven cases and was severe in two. Soreness of the tongue or mouth occurred in six. Anal irritation, which is perhaps the most annoying of all the side effects, occurred to some degree in fifteen cases. It varied from a mild itching to a severe inflammation. In one woman, there was an oozing dermatitis which involved the entire perianal and vulval areas. It began after only two days of treatment with one gram per day and required more than a week to subside after treatment was stopped.

As for terramycin, it seems less likely to produce nausea than aureomycin. Most and Van Assendelft[9] mention loose stools as the only complication. In our six cases, two complained of anal irritation, three of diarrhea, and two of abdominal cramps. In one case the diarrhea was severe.

Aureomycin, terramycin, and bacitracin suffer at present from one common defect. They are all expensive, more expensive than the standard amebacides. It is not my intention to discourage the use of these drugs by referring to their cost or their side effects. But the physician who uses them must have the disadvantages in mind in weighing his choice of remedy. And he must be briefed concerning the side effects so as not to be taken by surprise. These manifestations may really be troublesome and prove embarrassing both to the patient and physician. For example, one of our patients treated with terramycin developed severe diarrhea. Her comment was, "Before I started treatment I didn't feel so well, but now I really feel as though I have amebic dysentery."

Other Antibiotics: Chloramphenicol, which in general rather closely parallels aureomycin and terramycin in activity, is not useful in amebiasis. Most[3] reports failure in six cases treated. Spingarn and Edelman[12]

have had five failures in six cases treated and followed. We have observed a failure in one case so treated. Experiments in rats indicate that chloramphenicol is even less effective than penicillin and streptomycin, which are effective in these animals although they fail in vitro.[13] Polymyxin B failed in six of seven cases treated by Most and his collaborators.[3]

Dosage of Antibiotics in Amebiasis: Any suggestion as to the optimal dose of the antibiotics in amebiasis must, at present, be tentative. In the case of penicillin, where expense is no longer an important factor, it is best to give two million units over a period of four to five days and follow this immediately with amebacidal drugs. For bacitracin, I should suggest 20,000 units four times a day for about one week. For aureomycin, McVay and associates suggest 2 Gm. daily for seven days. Some patients will not, however, tolerate this dosage. Most[5] first used 2 Gm. daily but later suggested[8] that 1 Gm. daily might be adequate. At present, we are recommending for the average case, 2 Gm. daily for one or two days followed by 1 Gm. daily for the balance of one week. Obviously, with both bacitracin and aureomycin, it would be reasonable to use higher doses and longer treatment periods in relatively severe cases. The dose of terramycin should be at least equal to that of aureomycin. Most and Van Assendelft[9] suggest 2 Gm. daily for seven days in patients weighing more than 75 pounds, and 1 Gm. daily for seven days, in those weighing less.

Amebic Hepatitis: Up to this point, I have been considering only amebic infections of the colon. Our experience indicates that some degree of hepatitis occurs in about 5 per cent of cases. Sometimes this goes undetected and in mild cases it may clear up spontaneously following elimination of the colonic infection. In the severe cases, clinical evidence in the shape of pain over the liver, and fever, make the diagnosis more obvious. A very small number of cases actually go on to abscess formation.

We should not expect bacitracin to have any effect on hepatitis, since it is not absorbed. Actually, one of our bacitracin treated cases had a subacute hepatitis and, while his stools became negative, he showed absolutely no symptomatic improvement. The hepatitis did clear up with the administration of Aralen (chloroquine diphosphate).

Aureomycin may have a beneficial effect on amebic hepatitis. We have treated five cases. Three of them cleared up with no further ther-

apy. Two, however, required Aralen. Hughes[8] reports a failure of aureomycin in one case of amebic liver abscess, and Spingarn and Edelman[12] have told me of a case of amebic colitis with acute hepatitis, in which only the colitis responded to aureomycin; the hepatitis was cleared up with Aralen treatment.

Thus, some cases of hepatitis and probably all those with liver abscess will require treatment with emetine or Aralen. Those liver abscesses in which secondary infection is demonstrated should receive antibiotic therapy in addition to the amebacides. The agent selected will naturally depend on the bacteria found present.

Other Intestinal Protozoa

Aside from E. histolytica, the protozoa found in the human intestinal tract include the amebas, Endamoeba coli, Endolimax nana, Iodamoeba bütschlii, and Dientamoeba fragilis, the ciliate, Balantidium coli, and the flagellates, Trichomonas hominis, Chilomastix mesnili, and Giardia lamblia. G. lamblia is found in the small intestine; the others in the colon. D. fragilis, B. coli, and G. lamblia are pathogens; the remainder are apparently non-pathogenic.

Like the older amebacides, the antibiotics under discussion possess a degree of activity against most of the intestinal protozoa. In our experience, aureomycin made a clean sweep of the colonic parasites. No protozoa were found in our follow-up stool examinations in those cases in which E. histolytica was eliminated, except for G. lamblia. (This refers to E. coli in fourteen cases, Endolimax nana in eleven cases, Dientamoeba fragilis in three cases, Iodamoeba bütschlii in one case, and T. hominis and C. mesnili in one case.) Bacitracin was less efficient in this respect. Of five cases with D. fragilis, it failed in one. In two of four cases, it failed to eliminate E. nana, and it also failed to eliminate C. mesnili and T. hominis in the single case infected with both.

As to terramycin, Most and Van Assendelft[9] report that it failed to eliminate E. nana in two of nine cases, and T. hominis in the one case treated.

I have no data on the effect of antibiotics against Balantidium coli. In vitro studies reported from Chile[14] suggest that aureomycin may be active against this parasite.

As I have stated, Giardia lamblia, which inhabits the upper small intestine, stands apart from the protozoa which infest the large intestine.

It is not consistently affected by any of the standard amebacides. It is eliminated by quinacrine (Atabrine) with almost 100 per cent effectiveness. In our own cases G. lamblia was present in one case treated with bacitracin, two treated with aureomycin, and one with terramycin. It was still present after treatment. Not only was it still present, but in two cases the infection seemed to have become heavier. In addition, there have come to our attention two other instances, not in our own series, in which a profuse diarrhea with the stools swarming with G. lamblia, has occurred following aureomycin treatment. There are several possible interpretations of this phenomenon. The diarrhea may have been due to the aureomycin, the presence of G. lamblia being merely incidental. There may have been actual stimulation of growth of G. lamblia by certain growth factors said to be present in aureomycin. Or there may be a reciprocal inhibitory relation between G. lamblia and E. histolytica, so that one increases when the other is eliminated. Some of our experience with the standard amebacides suggest this last possibility. From the practical standpoint, in those cases in which both G. lamblia and E. histolytica are present, and the use of aureomycin or terramycin is contemplated, it would be advisable to administer atabrine first.

Trichomonas Vaginalis

Greenblatt and West[15] report activity of aureomycin and tyrothricin in vitro against Trichomonas vaginalis. They indicate that these agents are superior to streptomycin, chloromycetin, and penicillin in vitro. Nevertheless, they report encouraging results in clinical cases not only with aureomycin and tyrothricin, but also with bacitracin, chloromycetin and even penicillin in some cases. McVay and his associates[16] report more definite results with aureomycin. They treated fifty-three cases of trichomonas vaginitis with initial success in 47. Further therapy in those who relapsed appeared to clear up all the others. The oral administration of 2 Gm. daily for seven days had *no* effect. The favorable results were obtained with the local administration of 500 mg. of aureomycin in 2 Gm. of powdered talc. This was insufflated into the vagina on the first, second, fourth, sixth, and eighth day. Then one capsule of 250 mg. was inserted every night by the patient for two weeks. Side effects were limited to local itching.

Blood and Tissue Protozoa

Malaria: The antibiotics possess relatively little clinical useful-

ness in the treatment of infections with the blood and tissue protozoa. In human malaria penicillin is without effect. Streptomycin has a slight suppressive action on malaria in chicks but I know of no instances of its use in man. Aureomycin has been demonstrated to have definite antimalarial action both in animal malaria[17, 18] and in experimental human malaria.[19] It appears to have an effect on the tissue or exoerythrocytic parasites as well as on the erythrocytic forms. However, in the treatment of clinical attacks improvement occurred only after six days of therapy. Furthermore, it was obtained with tremendous doses—8 grams per day for seven days or 4 grams per day for fourteen days. These observations do not appear to be of any immediate value to the clinician. Terramycin is reported ineffective in one case of P. vivax infection.[20]

Trypanosomiasis: In African trypanosomiasis, or sleeping sickness, penicillin is apparently of no therapeutic value. In animal experiments streptomycin likewise seems devoid of effect. I know of no observations with aureomycin.

American trypanosomiasis, or Chagas' disease, has so far resisted the efforts of investigators to develop a useful therapeutic agent. Some field workers have claimed that penicillin is useful in the acute phase. Others report complete lack of effect. I have attended a laboratory worker accidentally infected with T. cruzi. He received penicillin after the diagnosis was made, but I could not convince myself that it had any real value. The acute phase is usually self-limited, so that any therapy given may be associated fortuitously with a decline in temperature and other improvement. In animals infected with T. cruzi, chloromycetin and streptomycin are ineffective.[21] Aureomycin renders the infection more severe than in infected but untreated controls.[22] Apparently this is one disease in which aureomycin seems contraindicated.

Leishmaniasis: In visceral leishmaniasis (Kala-azar) penicillin seems devoid of any fundamental clinical effect. However, in cases with marked oral ulceration, great benefit has been reported.[23] This effect is similar to that observed in the oral ulceration of neutropenic states, and is on secondary bacterial invaders. In cutaneous and mucocutaneous leishmaniasis there are some reports of improvement with penicillin, although no permanent cures are reliably reported. Here, too, the effect would seem to be on secondary infection.[24-26]

Toxoplasmosis: Frenkel[27] reports that bacitracin, aureomycin, chloro-

mycetin, and other antibiotics are ineffectual in the treatment of experimental toxoplasmosis. Summers[28] reports that aureomycin has some inhibitory effect on experimental toxoplasmosis, but is by no means curative. I have not found any record of the treatment of a human case with antibiotics.

Discussion

The practical clinical usefulness of antibiotics in the treatment of protozoal diseases seems at present limited to those which affect the large intestine and the vagina. These are areas in which there is a considerable bacterial population which may have a role in the pathogenesis. It is natural to consider the possibility that the antibiotics produce their effect indirectly through action upon the bacteria. The effectiveness of penicillin on the manifestations of amebiasis must be on such a basis. However, there is evidence that aureomycin and terramycin have a definite effect on the amebas. This is suggested by in vitro observations of Fuller and Faust[29] with aureomycin. It is further made plausible by the observations already mentioned of the effect of aureomycin on malarial infection, a protozoan infection not involving bacteria. Finally, we have observed in following our aureomycin and terramycin cases that in stools examined 48 hours after starting therapy the amebas usually show marked degenerative changes. Most and Van Assendelft[9] confirm this with respect to terramycin.

Leaving theory aside, it is evident that bacitracin, aureomycin, and terramycin may from the clinician's standpoint be listed as amebacidal drugs. Bacitracin is apparently less effective than the other two probably because it is not absorbed to any measurable degree. However, it is a useful reserve for resistant cases. The relative effectiveness of terramycin and aureomycin remains to be evaluated. Penicillin is not amebacidal, but is very useful in combination with standard amebacides in severe or resistant cases. Streptomycin has been reported to have a similar value[30] but it seems unwise to employ it because of its potential toxicity. In those cases in which there is hepatic involvement, it will usually be necessary to employ emetine or Aralen in addition to the antibiotic.

So much for the present status of antibiotics in amebiasis. I should like to take a minute to peer into the future and to speculate on the possibility that amebiasis may gradually become resistant to aureomycin and

terramycin. We know that emetine by itself does not cure amebiasis and that the repeated treatment of a patient with emetine alone may lead to a state in which further emetine injections are without effect. While some investigators deny the existence of emetine-resistant amebas, there is no doubt as to the clinical refractoriness of these cases. It has been reported that exposure of E. histolytica to sublethal concentrations of aureomycin in the test tube may result in an increased resistance to the drug.[31]

Many patients are now receiving relatively small doses of aureomycin and terramycin for respiratory and other, sometimes, ill-defined infections. These patients may harbor unrecognized or clinically inapparent amebic infections. It is conceivable that these exposures of the amebas to subcurative doses might lead to the emergence of resistant strains, so that eventually we will find terramycin and aureomycin of decreasing value.

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NEW AND OLD DEFINITIONS OF NORMAL BLOOD PRESSURE: CLINICAL SIGNIFICANCE OF THE NEWLY ESTABLISHED LIMITS*

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"In December, I caused a mare to be tied down alive on her back . . . having laid open the left crural artery about three inches from her belly. I inserted into it a brass pipe whose bore was 1/6 of an inch in diameter and to that, by means of another brass pipe which was fitly adapted to it, I fixed a glass tube, of nearly the same diameter, which was nine feet in length; then untying the ligature on the artery, the blood rose in the tube 8 feet 3 inches perpendicularly above the level of the left ventricle of the heart."[1] This skillful experiment, the first direct measurement of the blood pressure, was performed in 1733 by an English clergyman, Stephen Hales. Measurements of pressure that he carried out in sheep and dogs are still considered correct today. It is interesting to note that Hales estimated the blood pressure in man to be seven and one-half feet of blood expressed according to his system of measurement. This corresponds to about 170 mm. of mercury and, considering the crudeness of his methods and the fact that his work was done on experimental animals only, this was indeed a remarkably accurate deduction.

The measurement of blood pressure in clinical practice at the present day is a relatively simple procedure, easily performed on each patient. However, this procedure is the result of many studies and experiments, lasting almost a century, which dealt not only with the technical problems involved in devising an accurate and practical apparatus but also with the clinical value and interpretation of the blood pressure readings obtained. A few of the more important steps in the evolution of the blood pressure machine will be briefly presented.

The first instrument for indirect measurement of blood pressure in man, termed the Sphygmometer, was invented in 1834 by Julius Héris-

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Fig. 1. Hérisson Sphygmometer. 1834. A B half of a metal sphere with a membrane at its base; D capillary tube partly filled with mercury. Membrane placed on radial artery.

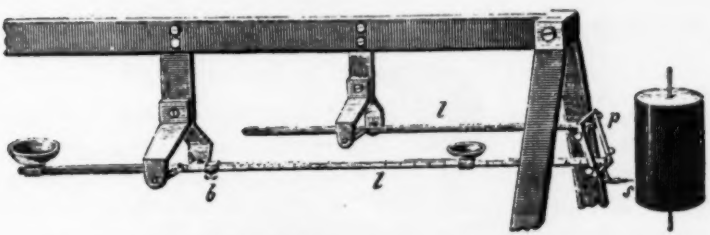

Fig. 2. Vierordt's Sphygmograph. 1855. Metal button (b) placed on on radial artery and weighted down by weights placed in two plates on metal bar (L). Writing point (S) inscribes radial pulse on Ludwig kymograph. Systolic pressure equals weight needed to obliterate radial pulse.

son,[2] a Paris physician (Fig. 1). By placing the membrane on the radial artery, Hérisson was able to discern the oscillations of the mercury column produced by the pressure in the radial pulse. From the amount of oscillation, Hérisson attempted to compute the intraarterial blood pressure. This was, of course, a very rough and inaccurate method.

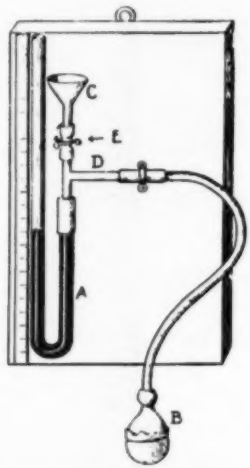

Fig. 3. Von Basch Sphygmomanometer 1876. A pelotte (B) consisting of a glass funnel covered with an elastic membrane is connected to a mercury manometer (A). Pelotte and tubing filled with water through glass funnel (C). Radial or temporal artery compressed with pelotte and at the instant that the pulse disappears, the systolic pressure is read off from the mercury manometer.

Fig. 4. Riva-Rocci Sphygmomanometer 1896. 5 cm. armlet used to compress arm. Readings about 10 per cent too high.

In 1855 Karl Vierordt,[3] a physiologist in Germany, devised an ingenious apparatus, the Sphygmograph (Fig. 2). This was the first instrument devised to register by an indirect method the pulsations in the radial artery and to estimate the systolic blood pressure by compression of this artery.

The first to make the indirect blood pressure reading a practical procedure in man was Von Basch,[4] a Viennese physician. By introducing an apparatus that could be used to estimate blood pressure by the average physician in his daily practice, Von Basch will always be remembered as the inventor and father of clinical sphygmomanometry. In 1876, he constructed an apparatus that was widely used (Fig. 3).

In 1896, an advance in clinical sphygmomanometry was made by the introduction of a new technique by Riva Rocci[5] (Fig. 4). For the first time an armlet was employed to compress the arm and this apparatus, as introduced by Riva Rocci, is the same as the one we use today except that a wider 12 cm. armlet is employed.[6]

Until 1904, the systolic pressure was determined by the palpatory method only and attempts were made to estimate the diastolic pressure by using radial pulse oscillations. In 1904 Korotkow,[7] a Russian physician, described the auscultatory method for determining the blood pressure. This is the method we use in our everyday clinical practice.

The Evolution of Blood Pressure Limits

In 1902, Potain published the first extensive work on blood pressure and its limits, "La Pression Artérielle de l'Homme."[8] Although his readings today are considered too high because of the technique employed, this book has great historical interest. This was the first time that blood pressure levels were correlated with factors which might influence the results, such as age, sex, weight, activity, altitude, etc.

The data which will be presented henceforth may be considered to be more or less accurate, as they have been obtained with standardized apparatus of the type used at the present time. In 1907, Theodore C. Janeway, of New York, using his own and some of his famous father's data, published a monograph entitled, "The Clinical Study of Blood Pressure."[9] He stated that a blood pressure above 145 mm. before middle age, or 160 mm. after this age, was definitely pathological if constantly present as the average reading.

About 1910 Brunton[10] of England, and Cook[11] of Johns Hopkins,

lowered these limits to 135 up to middle life, and 145 to 150 mm. thereafter. In 1915, Janeway[12] accepted these new criteria. We believe that 150 mm. mercury as the upper limit of normal systolic pressure in people over middle age became widespread largely because of Janeway's great reputation as an authority in this field.

In the past four decades, a number of life insurance companies have presented their statistics which have received wide publicity and which have played an important role in establishing the limits of normal blood pressure accepted today. In a study presented by Fisher,[13a] based on an analysis of 65,000 accepted risks, the maximum acceptable systolic pressure was placed at 131 mm. mercury at 16 years of age, and 151 mm. mercury at 65 years of age. In an insurance study of 150,000 men who were apparently healthy, Symonds[13b] concluded that the normal systolic blood pressure in males under 40 years, is below 140 mm. mercury. A number of other studies based on insurance company statistics have reported 150 mm. mercury as the maximal normal systolic pressure.[13]

There are several reasons for not accepting these insurance company statistics in clinical medicine. In the first place, they represent a very select part of the entire population. In addition, they are concerned primarily with group prognosis and mortality. For this reason, these data are not entirely applicable to the question of the relationship between blood pressure readings and the individual expectation of life.

All this material forms the basis for the accepted limits of blood pressure at the present time. However, it has been a common observation that people with blood pressure readings, above the commonly accepted limits, may live out their normal life span without complications related to their blood pressure. Bechgaard[14] followed 1,000 patients with blood pressures higher than 180 systolic and 100 diastolic, for a period ranging from 4 to 11 years. Some had pressures as high as 240/130! He found that half of them were in good health, and one-fourth were symptom-free at the end of this period. He noted that excess mortality from hypertension, definitely diminished with advancing age. Blood and Perera[15] likewise reported that long survival of people with so-called "high" blood pressure is far from rare and that elevated arterial pressure may not be associated with symptoms or rate of progression. Burgess[16] followed 100 patients with blood pressures of 180/100 or more, for at least eight years. He concluded that even severe hypertension, if it has been present eight years or more, and is not associated with well-estab-

lished cardiac or renal disease, usually does not indicate a poor prognosis. In fact, the patient may live to within three or four years of his normal life expectancy.

These results suggest that the accepted limits are too low and must be liberalized. Furthermore, a number of published studies of blood pressures in normal persons indicate that the limits of normality may be higher than we think. One of the first to publish data not conforming to the widely accepted limits of normal, 150/90, was Alvarez in 1923.[17] In a routine examination of approximately 6,000 young, healthy freshmen on entry into college, 22 per cent were found to have a systolic pressure above 140 mm. mercury. In a later study, Diehl and Sutherland[18] found that 11.5 per cent of 5,100 young college students without symptoms had a systolic pressure over 140 mm. mercury. These two large studies indicate that a number of presumably healthy young men have systolic blood pressures over 140 mm. mercury.

From the studies cited above (Bechgaard, Blood and Perera, Burgess, Alvarez, Diehl and Sutherland), we can see the handwriting on the wall. It seems essential to investigate and, if necessary, to change some of the old concepts concerning the limits of blood pressure in normal people. This is true not only of young and middle-aged people but particularly of the older age groups.

A number of studies have indicated that systolic blood pressure normally increases with age. A few of these will be mentioned. A study by Richter[19] in 1923, of 165 people 60 to 89 years of age, excluding those suffering from nephritis and heart disease, showed that the average systolic pressure increased with age from 138 to 161 mm. mercury.

A very important study was published in 1928 by Saller[20] in which he suggested that the increase in blood pressure in old age should be considered part and parcel of the aging process and may be likened to other changes, such as those in hair, teeth, eyes, libido, etc. He took the blood pressure in 4,200 patients in an out-patient clinic in Kiel, excluding all patients with heart or kidney disease, anemia, diabetes, fever and endocrinologic diseases. Saller's results are indicated in the following Table (Table I).

The salient finding of Saller was a gradual increase in blood pressure after the age of 47 so that between 68-89 years of age, the range of systolic blood pressure in the male was between 86-186 mm. mercury,

TABLE I—RANGES OF BLOOD PRESSURE AS DETERMINED BY SALLER IN 4,200 AMBULATORY PATIENTS

Age in Years	*Systolic B.P.*	
	Men	*Women*
21-35 } 35-47 }	98-144	{ 99-138 { 100-155
48-53	96-154	100-190
54-59	97-159	104-196
60-67	93-173	102-216
68-89	86-186	112-222

while in the female it was from 112-222 mm. mercury. Saller did not claim that all blood pressures lying within these limits were normal. It was his conclusion, however, that if the blood pressure was not outside these limits, one could not be sure that it would have any influence upon the length of life. Saller's study was a very extensive one and is cited in all papers on blood pressure in older age groups.

In an extensive study published in 1937, Kylin[21] agreed with the rule that the normal blood pressure may be estimated by adding the age in years to 100 mm. mercury. Furthermore, he gave as the maximum normal systolic blood pressure 170 mm. mercury. It is interesting that this rule, which enjoyed wide popularity for a time and then was discarded, is again coming into vogue as a rough "rule of thumb."

In 1943 Master, Marks and Dack[22] published findings in 15,000 blood pressure readings in persons over 40 years of age who formed a fairly representative group of the population. Using the definition of hypertension as 150/100 or over, they found that 1/3 of the male population and 2/5 of the female population 40 years of age and over are hypertensive. These proportions increase rapidly with age, so that high blood pressure is present in the majority of men 60 and over, and in women 50 and over. Therefore, they suggested that the usual definition of hypertension might have to be changed and the upper limit of normal in middle and later life revised upward. There have been a number of other studies tending to substantiate this point of view, e.g., Wishard,[23] Russek,[24] Gavey.[25]

George Perera and Dana Atchley[26] have emphasized the wide and inconsistent normal range of blood pressure. They point out that a

systolic blood pressure between 160-180 mm. mercury and a diastolic blood pressure between 90-100 mm. mercury may be found in a normal aged person. East and Bain[27] in 1948 employed a limit of 160 mm. systolic. while Evans[28] also in 1948, used 180 mm. systolic and 110 mm. diastolic.

The material which we have presented includes a large number of studies made by many physicians, in different countries, and in a large and varied section of the population. From their studies it is clear that new limits of what constitutes the normal systolic blood pressure must be established. The same considerations hold true for the diastolic pressure.

Diastolic Pressure

Before 1900 the main interest in blood pressure centered about the systolic pressure. In 1907, Janeway[9] stated that the systolic pressure alone was necessary for routine use and the diastolic only under certain circumstances. However today the pendulum has swung the other way, and more attention is paid to the diastolic pressure than to the systolic.

The insurance company statistics of the 1920's were the basis for the commonly accepted limit of up to 95 mm. mercury as the normal limit for diastolic pressure. However, in 75,000 university students, Boynton and Todd[29] found that about 4,500 (5 to 7 per cent) of these presumably healthy persons under 40 years of age had a diastolic pressure over 90 mm. mercury.

In the article by Master, Marks and Dack,[22] it is also shown that the diastolic pressure rose with age so that at ages 60-69, over one-quarter of those tested had a diastolic pressure over 95 mm. mercury. These studies indicate that the increase of the diastolic pressure with age is less marked than the systolic. This is in keeping with the well-known fact that the pulse pressure increases with age. It is evident that there is a need for reevaluating the criteria of what constitutes the normal limits of diastolic pressure as well as that of systolic pressure.

Presentation of New Limits

The preceding presentation has indicated the historical evolution of blood pressure limits up to the present day. It has been clearly shown that from time to time, clinicians and investigators, concerned with the average individual patient and not with data from selected groups, have

TABLE II—NORMAL RANGE AND LIMITS OF HYPERTENSION

Systolic	*Normal Range*		*Hypertension Lower Limit*	
Age	*Male*	*Female*	*Male*	*Female*
16	105-135	100-130	145	140
17	105-135	100-130	145	140
18	105-135	100-130	145	140
19	105-140	100-130	150	140
20-24	105-140	100-130	150	140
25-29	108-140	102-130	150	140
30-34	110-145	102-135	155	145
35-39	110-145	105-140	160	150
40-44	110-150	105-150	165	165
45-49	110-155	105-155	170	175
50-54	115-160	110-165	175	180
55-59	115-165	110-170	180	185
60-64	115-170	115-175	190	190

indicated the necessity of altering some of our concepts of what constitutes normal limits.

There are two methods available for the establishment of limits of normal blood pressure. One method is to follow the course of a large number of people with what are considered to be normal and elevated blood pressures, over many years, until death. The use of this method is limited by the extreme difficulty and expense of following very large numbers of people, year by year, until death. Even at postmortem examination, it is often very difficult to say whether the cause of death is related to the elevated blood pressure.

A second method, which we have employed, consists in surveying the blood pressure in large representative groups of the healthy population. This is a more advantageous technique. This method has been employed by many physicians to obtain averages, ranges and trends of blood pressure, correlated with age and sex, etc. However, none of these physicians have actually presented limits defining normal and abnormal blood pressure.

During World War II, the opportunity arose to obtain blood pressure readings in 74,000 persons who were in average good health and able to work regularly. These readings were obtained in industrial plants in various sections of the country in as representative a group as possible.

TABLE III—NORMAL RANGE AND LIMITS OF HYPERTENSION

Diastolic	*Normal Range*		*Hypertension Lower Limit*	
Age	*Male*	*Female*	*Male*	*Female*
16	60-86	60-85	90	90
17	60-86	60-85	90	90
18	60-86	60-85	90	90
19	60-88	60-85	95	90
20-24	62-88	60-85	95	90
25-29	65-90	60-86	96	92
30-34	68-92	60-88	98	95
35-39	68-92	65-90	100	98
40-44	70-94	65-92	100	100
45-49	70-96	65-96	104	105
50-54	70-98	70-100	106	108
55-59	70-98	70-100	108	108
60-64	70-100	70-100	110	110

Executive, clerical and manual workers, both skilled and unskilled, male and female, were used. As to the accuracy of the figures obtained, detailed correspondence with the numerous physicians involved, as well as personal observation, convinced us that the figures were reliable. Where any doubt existed the data were not used. The results of this survey were subject to statistical analysis and published recently by Master, Dublin and Marks.[30] The data actually tabulated covered a sample of 16,000 persons (8,000 men and 8,000 women). The age range was 16 to 65 years.

Tables II and III summarize the results of this study. They indicate the normal range of systolic and diastolic pressure by sex and age, and the limits beyond which the readings are probably abnormal.

From these tables it will be noted that the range of systolic pressure increases gradually with age. Also the range and limit of normal systolic pressure starts at a slightly lower level in women as compared to the men, and continues in this manner until the age of 40 when they are equal. After the age of 50 it is slightly higher in the women than in the men. Thus at 16 years of age the lower limits of systolic hypertension for the male is given as 145 mm. mercury (normal range 105-135) and in the female it is 140 mm. mercury (normal range 100-130). At 55-59 years

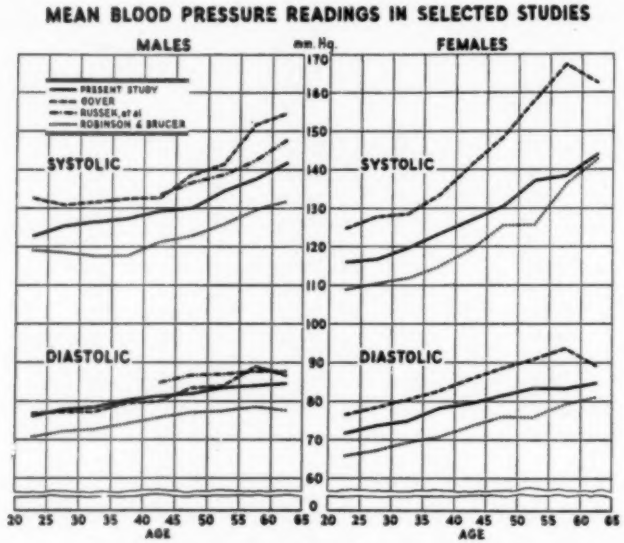

Fig. 5. Mean blood pressures in several selected studies.[24,31]

of age the lower limit of systolic hypertension for the male is 180 mm. mercury (normal range 115-165) and for the female it is 185 mm. mercury (normal range 110-170). All the cases falling between the maximum value given for the normal range and the lower limit of systolic hypertension are considered as borderline cases. They may belong to the normal or hypertensive group depending upon their clinical status (history, physical examination, cardiac enlargement, kidney disease, etc.).

The same gradual increase may be noted in the diastolic readings, but here the increase is less marked than in the case of the systolic pressure. Thus at 16 years of age 90 mm. mercury (normal range 60-86) and at 64 years of age 110 mm. mercury (normal range 70-100) are given as the lower limits of diastolic hypertension.

In comparing our new limits with those given by two other investigators in this field,[31] it will be evident, from the following figure, that our limits occupy a midposition between the other two (Figure 5).

Discussion

The predominant ideas about what constitutes normal blood pressure readings have been built up largely by data relating blood pressure readings to group mortality figures. These studies have been produced mainly by the life insurance companies. We have shown that the practice of using selected group mortality to delineate what constitutes normal limits for blood pressure, cannot be employed in the analysis of the significance of the blood pressure reading in the individual case. From time to time, clinicians have pointed out the fallacy of accepting these rigid and fixed criteria to delimit the normal from the pathological. Accordingly, the problem of obtaining new limits of normal and abnormal blood pressure is paramount. We have analyzed and presented data based on 74,000 blood pressure readings, which raise the normal limits of blood pressure usually accepted today.

In evaluating blood pressure readings, based on these new limits, it is to be emphasized that these readings must not be interpreted too literally. The blood pressure is only one factor to be considered in the determination of the clinical status of the patient and it must be evaluated in the light of the history, physical examination, eyeground changes, x-ray examination, functional tests of the heart, etc.

The acceptance of the new limits may have an effect in many fields. In the medical field it may be necessary to revise much data based on the correlation between moderate "hypertension," according to the old criteria, and various conditions—for example, coronary artery disease and coronary occlusion, cardiac enlargement, arteriosclerosis and diabetes. Many of these supposed relationships are being studied, using the new limits, and will be presented at a future date.

In other fields too, the importance of the new limits is considerable. At the present time, not only physicians but also laymen have become alert to the importance and significance of the blood pressure reading. In clinical practice, every physician sees many patients who are greatly disturbed by blood pressure levels which are moderately "hypertensive." With the new limits, these patients will be relieved by the knowledge that their blood pressure may be within normal limits and is not incompatible with an average expectation of life. In addition, much therapy which is being employed to try to lower the blood pressure of these patients will no longer be considered necessary.

The application of the new limits must also have widespread effect in industrial and military medicine, and in the life insurance field. In the industrial field, many men, particularly those over middle age, who have been rejected because of so-called hypertension, will have the opportunity to become gainfully employed. Present concepts of hypertension, as related to Workmen's Compensation, will have to be revised. These changes will mark important gains for the individual and for the community in which he lives. In the military field a number of rejectees may be considered fit for service when the new criteria are used; this will allow better utilization of our manpower.

It is not at all our intention to minimize the importance of true hypertension and its complications. The effects of the malignant form, in particular, are only too well known. There must be no slackening of the effort to learn the causes of high blood pressure and to develop a prevention or cure.

Conclusion

A short history has been given of the development of our knowledge of blood pressure and apparatus used to register it.

A historical and critical evaluation of the development of blood pressure limits has been presented and new limits of normal blood pressure proposed. The importance of application of these new limits in various fields has been emphasized.

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THE TREATMENT AND PROGNOSIS OF CONVULSIVE DISORDERS IN CHILDREN*

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THIS brief presentation will be confined to a consideration of the practical aspects of treatment of convulsive disorders of children, and to the question of prognosis. As regards therapy, only those anticonvulsive drugs in common use will be discussed, as well as certain psychogenic factors which I believe are of equal importance in reaching a satisfactory therapeutic solution.

During the last ten years, i.e., since the introduction of more effective anticonvulsive drugs, we have not had occasion to refer a single child for surgical removal of an epileptogenic cerebral focus. This doesn't mean that the indications for surgical treatment do not exist. It simply indicates the extremely limited need for this therapeutic approach in children. Also, during this same period, we have completely given up the use of the ketogenic diet for the control of convulsive manifestations. Under the most ideal conditions and in a limited number of patients, it may have proved equally effective as drug therapy. However, the practical difficulty of maintaining the ketogenic diet in young children for any considerable period, as well as the emotional problem arising as a result of so restrictive a regime, have greatly limited its usefulness.

The four drugs in common use are: phenobarbital, dilantin, mesantoin and tridione. In most cases, these drugs are used in various combinations. The selection of drugs depends primarily on the clinical manifestations and the type of EEG abnormality exhibited. This is summarized in Table I. The table lists the most common types of epileptic manifestations. These need no detailed discussions. The three symptoms, namely: the simple or staring type of petit mal, myoclonic jerks, and akinetic seizures are grouped together as the "petit mal *triad*." All three are charac-

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TABLE I—CHOICE OF DRUG ON BASIS OF CLINICAL MANIFESTATIONS

Type of Spell	*Phenobarbital*	*Dilatin*	***Mesantoin*	*Tridione*
Grand Mal	+	+	+	
Petit Mal	+			+
Simple				
Myoclonus	+	+		+
Akinetic	+			+
Psychomotor	+	+	+	
Focal	+	+	+	
*Starting dose	1-2	2-3	1-2	15-20
Maximum dose	5	10	5	50(?)
Average	5	5-6	3	25-30

* Expressed in mgms. per kgm. per day.
** As supplement to Dilantin.

terized by a type of seizure that is extremely short, being measured in seconds, and also exhibit as part of their EEG abnormality, the spike and dome type of complex. In older children the myoclonic jerk usually involves a single muscle or muscle group. In very young infants, in addition, one may see mass myoclonus in which a major part of the entire skeletal musculature is involved in the convulsive reaction. We have not seen this in children over two years of age. It has much more serious implications than do the other two members of the triad as regards underlying pathology and prognosis. The akinetic type of reaction manifests itself as a complete loss of postural control. If upright, the child suddenly slumps over, usually quickly resuming its previous state of activity. Only rarely do any of the petit mal triad persist beyond the preadolescent or adolescent periods. It should be possible to control most of these cases with adequate therapy so that, within a reasonable period of time, there is little significant interference with the normal activity of childhood. Psychomotor epilepsy, in which relatively complicated motor activity takes place of which the patient is unaware, is relatively rare in children, making up less than 3 per cent of epileptic manifestations in our clinic. However, it represents the most difficult type to treat at the present time. It is estimated that approximately 60 per cent of the epileptic manifestations are of the uncomplicated grand mal type, about 25 per cent represent the petit mal triad. The remaining number include those with combined grand mal and petit mal spells as well as the more uncommon types of reactions.

Drug Therapy

It will be noted in Table I that, of the drugs in common use, phenobarbital has the widest range of usefulness. It can be employed with profit in every child with convulsive disorder, regardless of manifestation. In a small number, it can accomplish satisfactory control when employed alone. It is also the least toxic. Phenobarbital owes its greater usefulness, I believe, to the fact that of all the available antiepileptic drugs, it alone has therapeutic sedative qualities in addition to its anticonvulsive activity. We have made it a practice, with few exceptions, to start with phenobarbital alone, regardless of the type of epileptic manifestation. The starting dose, as a rule, is approximately 2 mgms. per kilogram of body weight per day. It has been our experience that doses in excess of 5 mgms. per kilogram per day, will result in undesirable degrees of drowsiness if continued for relatively prolonged periods. Reëvaluation of the case is carried out after varying intervals, depending on the course, in order to determine whether dilantin or tridione is to be added. In the case of uncomplicated petit mal, tridione is added only if the number of spells is such as to significantly interfere with the child's normal activity. If the spells are relatively infrequent and do not result in any significant handicap under the conditions of the child's usual environment, we feel that it is unnecessary to use tridione, regardless of the EEG findings. The potential toxicity, even though slight, and the necessity for continued and close observation of the peripheral blood, are disadvantages that, I believe, outweigh any possible beneficial effects in relatively mild cases. However, this degree of clinical mildness is relatively uncommon. The greater number of cases will exhibit numerous petit mal spells which tend to interfere with normal childhood activity and require the more effective assistance afforded by tridione. The starting dose of tridione is approximately 15-20 mgms. per kilogram per day, increasing at weekly intervals, if necessary, to about 40-50 mgms. per kgm. The toxicity of tridione is, presumably, not directly related to total dosage, as is usually the case with phenobarbital and dilantin, but probably depends on a specific and individual sensitivity. The upper limit of tridione dosage has not been completely explored. We have used this drug in unusual circumstances at levels of 75 mgms. per kgm. per day without untoward results. The average dose will usually be found at 25-30 mgms. per kgm. Although myoclonic epilepsy is part of the petit mal triad, we

prefer to add dilantin first to the phenobarbital in this condition; and then, if necessary, tridione can also be given. This is especially true in very young infants with mass myoclonus. Dilantin in combination with phenobarbital is used for grand mal, psychomotor and focal seizures. The starting dose for dilantin is about 2-3 mgms. per kgm. per day. This can be increased at weekly or bi-weekly intervals up to approximately 8 mgms. per kgm. Doses in excess of 10 mgms. per kgm. result, in a large proportion of the cases, in rather characteristic toxic signs such as ataxia and a peculiar euphoric behavior. The appearance of these signs simply requires a 20 to 30 per cent reduction in the total dosage. It is inadvisable, and may be dangerous, to completely withdraw dilantin under these conditions since this may lead to serious exacerbation of spells and occasionally to status epilepticus. The gum hyperplasia, which is seen in variable degree in 50 to 60 per cent of individuals receiving dilantin, is rarely severe or disfiguring to the extent requiring withdrawal of this drug. Regular dental prophylaxis will minimize this condition. Mesantoin is a useful drug within certain limitations. Its potential toxic properties make it necessary, as is the case with tridione, to carry out frequent examinations of the peripheral blood, and this disadvantage outweighs the advantages that have been described for mesantoin as compared to dilantin. Actually, our experience to date, as regards its anticonvulsive properties, does not indicate any significant superiority. We, therefore, do not feel, at least at present, that it should replace dilantin. Our use of mesantoin is confined to those cases already receiving what we believe is maximum dilantin and phenobarbital dosage, but who still require additional anticonvulsive medication. In these cases, we have supplemented with mesantoin, starting with about 1-2 mgms. per kilogram, increasing, as indicated, up to a tentative maximum of 5 mgms. per kilogram per day. This regime has frequently resulted in definitely improved anticonvulsive control.

Status epilepticus represents one of the few emergencies in the treatment of convulsive disorders. The earlier treatment is started, the more satisfactory and prompt is the response. In our experience, the most effective drug, if used in adequate dosage, is sodium phenobarbital administered by intramuscular injection. The starting dose is 5-7 mgms. per kgm. depending on severity and interval of time since onset. Additional injections of 2-3 mgms. per kgm. at 20-30 minute intervals are given as needed. It is unusual for the total 24-hour dosage of the drug

to exceed 12-15 mgms. per kgm. The average amount usually approximates 10 mgms. per kgm.

Psychogenic Factors

There are few conditions that the pediatrician encounters in which greater potentialities for the development of emotional disorders exist than epilepsy. Morover, in an appreciable number of these children, the social maladjustments resulting from these emotional and behavior disorders, present a much more serious and difficult problem to treat than do the spells themselves. Consequently, efforts directed toward the prevention of serious emotional and behavior disorders must be made an integral part of the handling of the epileptic child as is drug therapy.

Personality and behavior difficulties in the epileptic child can usually be traced to parental and family tensions arising from unresolved anxiety states developing soon after the diagnosis is suspected by the family or made by the physician. In older children, problems relating to or arising in the school and community further complicate the picture. Much of this difficulty, both in the home and community, is due to misconceptions and unwarranted apprehensions concerning certain of the clinical aspects of epilepsy. For instance, a large proportion of both lay and professional individuals continue to believe that every convulsion produces some degree of irreversible cerebral damage and that sooner or later this will lead to mental deterioration unless immediate and complete control of spells is achieved. This is untrue. So is the belief so frequently expressed, that the spells, per se, or perhaps the cerebral dysrhythmia will invariably give rise to the constellation of behavior abnormalities loosely labelled "epileptic personality." Actually, this represents a nonspecific manifestation resulting from continued mismanagement of the child in its familial and community environment. The same type of response might be expected in any child with a chronic disease, equally mishandled. These, and many other concepts that need no detailed listing, must be clarified for the parents, particularly the mother, who must serve as the means by which the physician attempts to influence the child's environment both in the home, community, or school. Prognosis can then be explained to the parents, not solely in terms of spells, but in the broad aspects of future social adjustment. Immediate and complete control of spells cannot, as a rule, be promised.

However, the possibility of future spells must not be allowed to significantly interfere with a normal daily program. The epileptic child should be allowed and encouraged to participate in practically all the activities suitable for his age. Certain calculated risks must be taken, especially as regards possible accidents. These can be minimized, however, without drawing too much attention to the child. We do not believe strenuous activities in any way adversely influence the occurrence of spells. Also, there is little the mother can really accomplish as regards spell control by manipulation of diet (aside from the rigid ketogenic diet); by excessive attention to bowel habits; by readjustment of sleep and rest programs; and the many other minor annoyances that anxious parents inflict on children in this and comparable conditions. Discussions along these lines with the mother, at regular intervals, are admittedly time consuming but of utmost importance if future difficulties are to be avoided. The degree of effectiveness with which members of the family, the immediate neighborhood, and the school handle the problem of the epileptic child is in direct relationship to the adequacy with which we can make the mother appreciate the importance of the concepts just discussed. It should not be surprising to pediatricians that this aspect of treatment, which is essentially psychotherapy, is mediated almost entirely through environmental control. Only rarely have we found it necessary to institute direct psychotherapeutic procedures with the child. Whenever indicated, this has been done, largely by means of simple interview techniques during the regular clinic visits. Only in the occasional case, has a more specialized approach been sought through the Children's Psychiatric Clinic.

Fortunately, the need for institutionalization of an epileptic child of normal intelligence arises infrequently. I say "fortunately" because suitable residential schools for this purpose, and within the financial means of most people, are few indeed. With rare exceptions, state supported schools for epileptics are primarily the training schools for mental defectives. These are geared for the training and custody of the mentally handicapped and totally unsuited to house and care for children of normal intelligence. Every effort should be made to discourage this type of solution. The epileptic spells per se or their control are rarely the prime causes for considering the removal of the child from the home. In the majority of cases, it is difficulties along psychogenic lines, in the form of emotional and behavior problems that raise the

question of institutionalization. Occasionally, the use of foster homes can be recommended in suitable cases. These, however, are admittedly difficult to find. We are also witnessing a tendency for some states to develop publicly supported child study homes or similiar units for the disturbed child that may help meet this problem.

Prognosis

There have been many reports in the literature regarding the results of treatment of children with convulsive disorders, involving current drug therapy as well as dietary procedures. These are difficult to evaluate, primarily because the criteria for satisfactory control is almost entirely confined to a consideration of the incidence of spells either in absolute numbers or relative terms. Unfortunately, this only presents part of the picture as I have attempted to indicate. It is apparent that an emotionally well-adjusted child having three to five grand mal spells a year is better off than one having only one or two spells a year but seriously handicapped by personality and behavior disorders resulting from untreated tensions in the home directly related to the epileptic state. With this in mind, a survey was made of all children with grand mal or combined grand mal and petit mal epilepsy treated in our clinic in New Haven since 1940. All cases were included for whom an adequate follow-up was available for at least one year after treatment was instituted. Reasonably accurate records of seizures, school progress and home and community adjustment were also available. Most of this information had been obtained from the parents and was recorded in the clinic charts. In some cases this was supplemented by social service workers and school authorities. A good result was arbitrarily defined by the following criteria: 1) less than 5 grand mal seizures per year. When combined with petit mal spells, the latter were of such a frequency and nature that they in no way interfered with normal activity according to the parents and teachers; 2) a completely satisfactory school and community adjustment according to the age and capabilities of the child; 3) expression of satisfaction on the part of the parents as regards the control of spells. The results of this study are summarized in Table II. A total of ninety-three children are included in the group surveyed. Of these, sixty-nine were diagnosed as idiopathic epilepsy, of which fifty-four had only grand mal spells, and fifteen, combined grand mal and petit mal epilepsy. Thirteen cases were due to congenital

TABLE II—GRAND MAL EPILEPSY*

Etiologic Factors†	*No. Cases*	*Therapeutic Results* *Good (%)*	*Poor (%)*
Idiopathic			
All cases	69	82.6	17.4
Positive family history	22	100.0	0.0
Negative family history	47	78.7	21.3
Normal EEG	23	86.9	13.1
Abnormal EEG	43	81.4	18.6
Congenital Cerebral Defect	13	30.7	69.3
Birth Trauma	11	63.6	36.4

* Does not include 3 cases postinfectious and 3 cases of postnatal trauma.
† 54 Grand mal.
15 combined grand mal and petit mal.

cerebral defects, the majority being associated with varying degrees of mental deficiency. Eleven cases were due to birth trauma. Not included, because the numbers were too few to separately classify, were three cases of post-infectious etiology and three cases of post-natal trauma. The results of these six cases were not unlike the birth trauma group. Of the sixty-nine cases with idiopathic epilepsy, about 83 per cent had a good therapeutic result. About 30 per cent were completely free of spells, while most of the remainder had less than three grand mal spells during the preceding year. It is of interest that the twenty-two cases with a positive family history of idiopathic epilepsy, all had good results as compared to poor results in 21 per cent cases with a negative family history. Also of interest is the observation that in about one-third of the cases, a normal EEG had been obtained. In this group, however, the results could hardly be considered significantly better than in those with abnormal EEG. Further analysis also indicated that as regards prognosis, there was no significant difference between those whose spells started prior to one year of age as compared to those whose spells started later in life. Also, when treatment was instituted within one year of the onset of spells, the results were somewhat better than when therapy was started later. (87 per cent good results as compared to 71 per cent.)

In the group with congenital cerebral defects, the results in general, were poor, only 30 per cent having a satisfastory result as regards the

epileptic status. The birth trauma group had somewhat better results with 60 per cent achieving satisfactory control.

Although not included in this survey, our results in children with uncomplicated petit mal epilepsy of the simple staring type, was universally good; about 90 per cent, sooner or later, achieving satisfactory or even complete control, especially in children with normal mental status. On the other hand, considerable difficulty with poor to indifferent results were observed with many children, especially under two years of age with the akinetic or mass myoclonic type of spells. A large proportion of these children were also mentally defective.

Summary

This paper discusses the practical aspects of the treatment of convulsive disorders in children. The use of the four most commonly employed anticonvulsive drugs is described including phenobarbital, dilantin, mesantoin, and tridione. The importance of careful consideration of environmental factors such as the home, school and community is stressed. Of equal importance to drug control in eventual social adjustment, is the prevention and treatment of emotional and behavioral disorders. The results of a survey of a fairly large group of epileptic children treated in the manner described, suggests a much more hopeful attitude towards prognosis in these children than has been frequently expressed.

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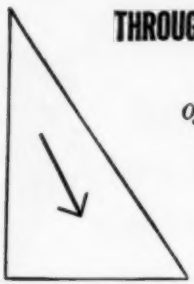

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*Kirwin, T. J., Lowsley, O. S., and Manning, J.: Effects of Pyridium in certain urogenital infections, *Am. J. Surg.* **62**: 330-335, December 1943.

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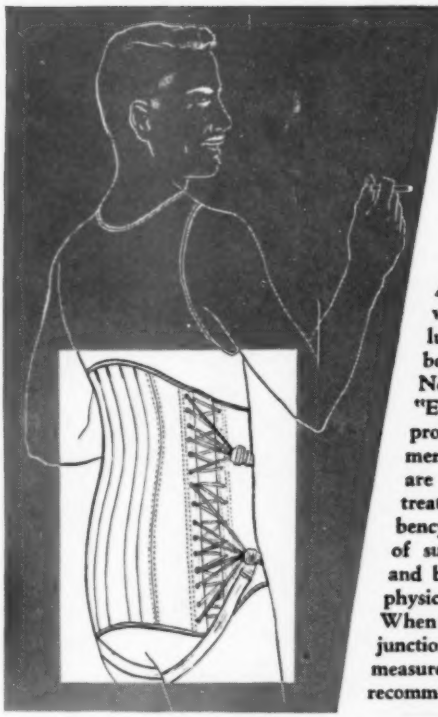

LUMBOSACRAL SUPPORT

An Orthopedic Surgeon* in writing on the treatment of lumbosacral disorders in his book Backache and Sciatic Neuritis states as follows:— "Every patient should be given prolonged conservative treatment before radical measures are considered. Non-operative treatment consists of recumbency in bed, the application of support (adhesive strapping and belts of various types) and physical therapeutic measures. When backache at the lumbosacral junction is uncontrollable by such measures, a fusion operation is recommended."

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Philip Lewin, M.D., F.A.C.S.
Backache and Sciatic Neuritis,
Chapter XXXIX, Page 580
Published 1943 by Lea & Febiger, Philadelphia

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$\log \frac{S}{S-x} - 0.4343\frac{x}{S} = \frac{c}{K}$

It's *simply* physical

$\frac{S}{S-x} = KC$

$\frac{S}{S-x} - Ax = KC$

$\frac{a-x}{v} S = Ke^{\frac{A(S-x)}{S}x}$

$K - \frac{dx}{dc} = \frac{S-x}{x^n}$

$\frac{S}{S-x} - Ax - KC$

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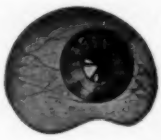

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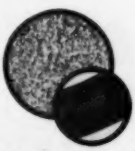
1. Clark, Le M.: The Vaginal Diaphragm. St. Louis, C. V. Mosby Company, 1938; p. 43.
2. Dickinson, R. L.: Techniques of Conception Control. Baltimore, Williams & Wilkin Company, 1930; p. 17.



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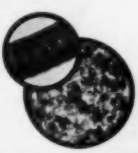

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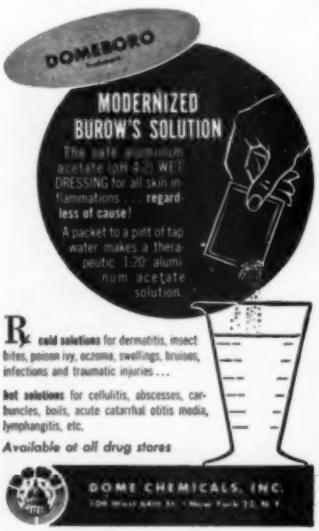
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1. Heinberg, C.J.: Eye, Ear, Nose & Throat Monthly 30:31 (Jan.) 1951.

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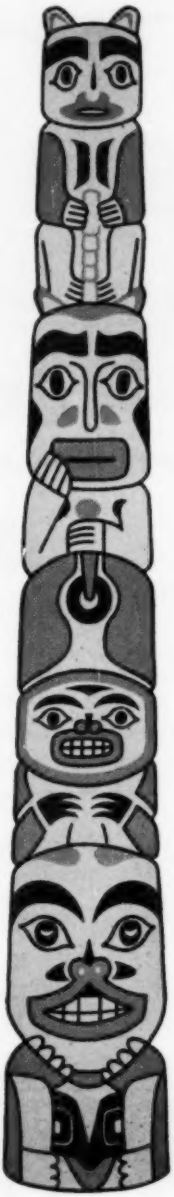

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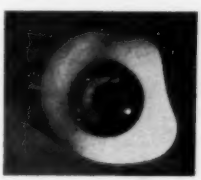

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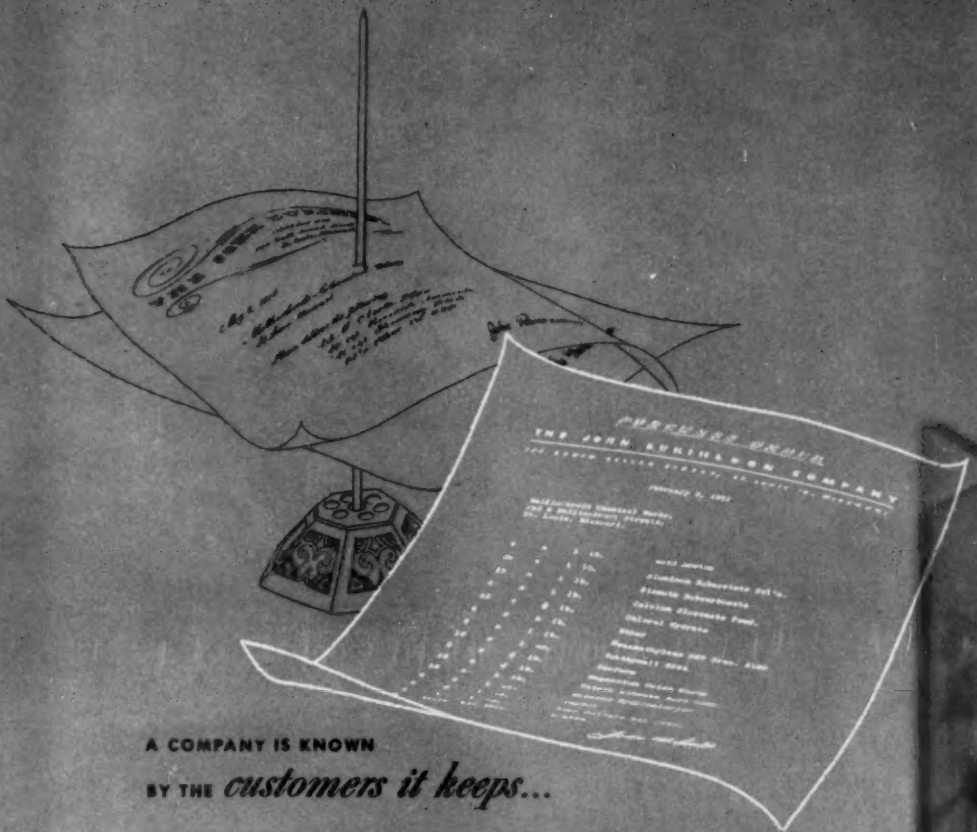

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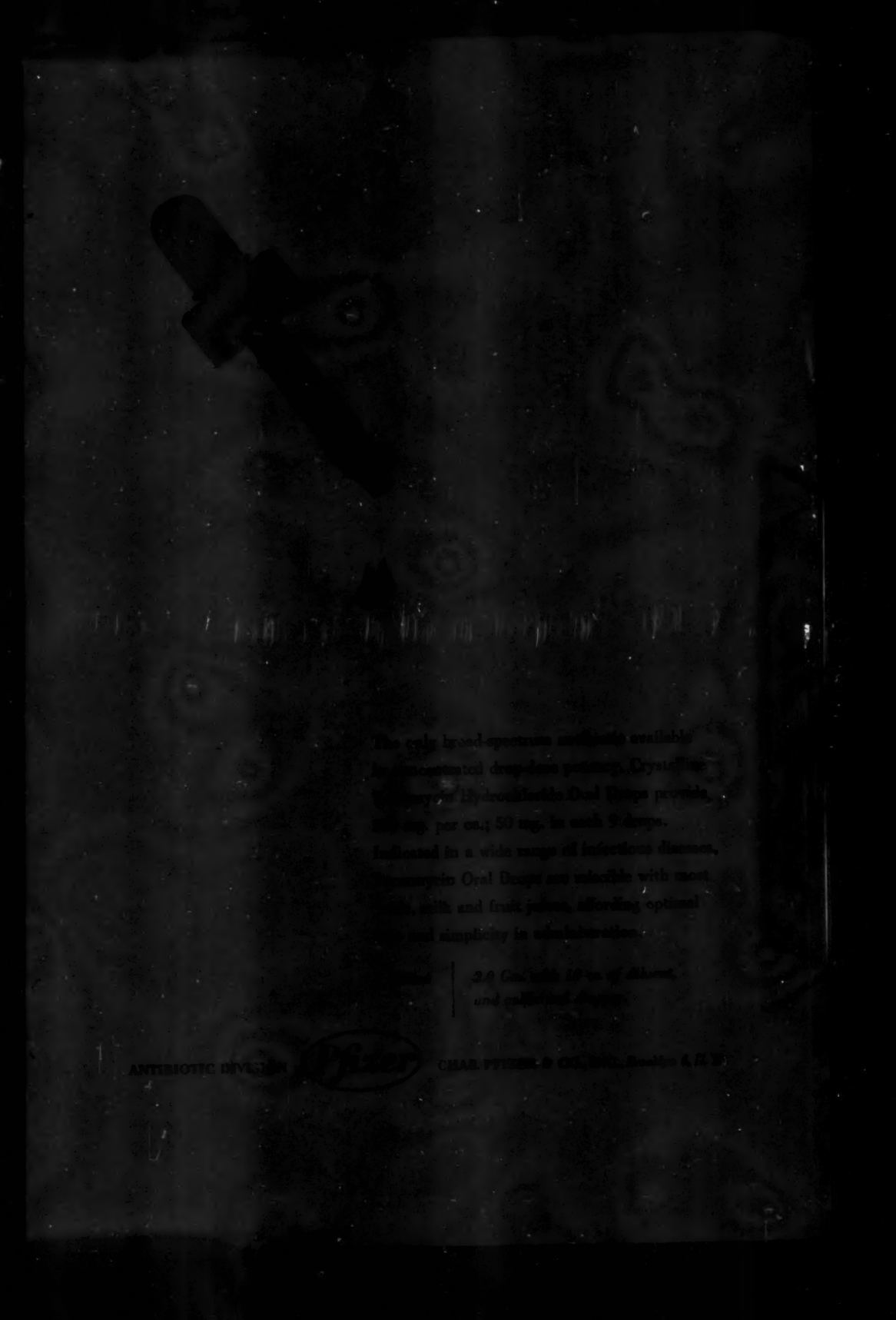
*Overman, W. J.; Gordon, W. H., and Burch, G. E.: Tracer Studies of the Urinary Excretion of Radioactive Mercury following Administration of a Mercurial Diuretic, Circulation *1*:496, 1950.

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